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(71) Applicant: FUJISAWA PHARMACEUT CO

LTD

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(72)Inventor: OKUBO MITSURU

TAKAHASHI FUMIE YAMANAKA TOSHIO SAKAI HIROYOSHI KATO MASAYUKI

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(54) BETA-ALANINE DERIVATIVE AND ITS PRODUCTION

(57)Abstract:

PURPOSE: To obtain a new β -alanine derivative being a glycoprotein IIb/IIIa antagonism, an platelet aggregation suppressor and a fibrinogen platelet-binding suppressor and useful for preventing and treating thrombotic diseases.

CONSTITUTION: This new β -alanine derivative is expressed by formula I [R1 is a substitutable N-containing a cycloalkyl; R2 is a (protected)carboxy;

A1 is a low alkylene, a lower alkanyl-ilidene or a lower alkenylene which may each be substituted); A2 is a lower alkylene; A3 is a substitutable lower alkylene; formula II is formula III (formula III is a

substitutable N-containing heterocyclic group); X is O,

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S or NH; Y is NH; Z is formula IV to formula VI (R3 is H or a lower alkyl); (1), (m) and (n) are each 0 or 1] and its salt, e.g. N-[(R)-1-{3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-2 (S)-acetylamino- β -alanine. The compound of formula I where (m) is 0 is obtained by reacting a compound of formula VII or its reactive derivative with a compound of formula VIII or its reactive derivative.

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(71) Applicant (for all designated States except US): FUIISAWA With international search report.

(71) Applicant (for all derignated States except US): FUIISAWA PHARMACEUTICAL CO. L.D. [JJJT]; 4-7. Doshomachi 3-chorac, Chuo-lu, Osake-ati, Osake 541 (JP).

(72) Inventors; and (73) Inventors; and (75) Inventors; and (77) Inv

(54) TILL: N-(3-PTERIDINYLCARBONYL)-BETA-ALANINE DERIVATIVES AS PAF ANTAGONISTS

(57) Abstract

This invention relates to βalanine derivatives represented by
com.i.u. (l), wherein earls symbol, its a defined in the specification and planmaceut.'s lly acceptable salt thereof which is β.); co-

R1-(x1-A1-C-(x1-)

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bite sait thereof which is glytonprocin IPAIIs anagonist, inchinic of 60 yed placelets aggregation and inhibit; of the binding of firminogen to blood platelets, to processes: for the preparation dereof, to a plarmaceutical composition comprising the same and to a method for the prevention and/or treatment · ? discuss indicated in the specification to a human being or an animal.

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DESCRIPTION

N-(3-PIPERIDINYLCARBONYL)-BETA-ALANINE DERIVATIVES AS PAF ANTAGONISTS

TECHNICAL FIELD

The present invention relates to β -alanine derivative inhibitor of blood platelets aggregation and inhibitor of salt thereof which is glycoprotein IIb/IIIa antagonist, particularly, it relates to β -alanine derivative and a and a pharmaceutically acceptable salt thereof. More the binding of fibrinogen to blood platelets.

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BACKGROUND ART

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In European Patent Application No. 512,831 Al, there are disclosed fibrinogen receptor antagonists.

In European Patent Application No. 445,796 A2, there disclosed inhibitor of blood platelets aggregation.

DISCLOSURE OF INVENTION 20

present invention relates to β -alanine derivative platelet and a sait thereof. More particularly, it relates to ... glycoprotein IIb/IIIa antagonist and inhibitor of \$-alanine derivative and a salt thereof which is aggregation, and useful as : and perference

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infarction, etc.), coronary thrombosis, etc.]; ischemic brain diseases [e.g. cerebral infarction (e.g. cerebral thrombosis; arterial sclerosis; ischemic heart diseases unstable anging pectoris including imminent infarction, a drug for the prevention and/or the treatment of diseases caused by thrombus formation such as arterial cerebral embolism, etc.}, transient cerebral ischemia etc.), myocardial infarction (e.g. acute myocardial le.g. angina pectoris (e.g. stable angina pectoris, thrombosis (e.g. acute cerebral thrombosis, etc.),

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pulmonary embolism"etc.); peripheral circulatory disorder angiopathy, diabetic neuropathy, etc.), phlebothrombosis transient ischemic attack, etc.), cerebrovascular pulmonary vascular diseases (e.g. pulmonary thrombosis, obliterans (i.e. Bürger's disease), Raynaud's disease, spasm after cerebral hemorrhage (e.g. cerebrovascular (e.g. deep vein thrombosis, etc.), etc.] or the like; spasm after subarachnoid hemorrhage, etc.), etc.]; [e.g. arteriosclerosis obliterans, thromboangiitis complication of diabetes mellitus (e.g. diabetic

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angioplasty (PTCA), restenosis and/or reocclusion after restenosis and/or reocclusion such as restenosis and/or a drug for the prevention and/or the treatment of reocclusion after percutaneous transluminal coronary the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.) or the like;

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a drug for the adjuvant therapy with thrombolytic drug (e.g. TPA, etc.) or anticoagulant (e.g. heparin, etc.);

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a drug for the prevention and/or the treatment of the thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery hemodialysis, etc.], transplantation, or the like; (e.g. open heart surgery, pump-exygenator, etc.)

disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation a drug for the prevention and/or the treatment of a drug for inhibiting of metastasis; or the like. (e.g. nephritis, etc.), immune diseases, or the like;

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expected to be useful as an inhibitor of cell adhesion and The \beta-alanine derivative of the present invention is so is expected to be useful as

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disseminated int "vascular coagulation (DIC), thrombotic a drug for the prevention and/or the treatment of

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thrombocytopenia, essential thrombocytosis, inflammation a drug for inhibiting of metastasis; or the like. (e.g. nephritis, etc.), immune diseases, or the like;

to provide eta-alanine derivative or a salt thereof which is Accordingly, one object of the present invention is useful as stated above. Another object of the present invention is to provide processes for preparation of said β -alanine derivative or a salt thereof.

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provide a pharmaceutical composition comprising, as an active ingredient, said β -alanine derivative or a salt A further object of the present invention is to thereof Still further object of this invention is to provide methods of using said β -alanine derivative or a salt thereof for the prevention and/or the treatment of aforesaid diseases in a human being or an animal.

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The object \$-alanine derivative of the present invention can be shown by the following formula (I)

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wherein R¹ is N-containing cycloalkyl which may have one

or more suitable substituent(s), \mathbb{R}^2 is carboxy or protected carboxy,

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lower alkenylene, each of which may have is lower alkylene, lower alkanyl-ylidene or one or more suitable substituent(s),

A² is lower alkylene,

is lower alkylene which may have one or more

suitable substituent(s),

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is a group of the formula

heterocyclic group which may have one or is N-containing more suitable substituent(s)), wherein

is O, S or NH,

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is NH

is
$$\begin{pmatrix} c_{-N} \\ l \\ l \end{pmatrix}$$
 $\begin{pmatrix} l \\ l \\ l \end{pmatrix}$

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(, m and n are each the same or different an wherein R³ is hydrogen or lower alkyl), integer of 0 or 1,

or a pharmaceutically acceptable salt thereof.

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The object compound (I) or a salt thereof can be prepared by the following processes.

Process 1

¹-(х), ¬А¹-соон

or its reactive derivative at the amino group (III) or its reactive derivative at the carboxy group or a salt thereof (II)

or a salt thereof

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$$R^{1-(X)} \frac{1}{\ell} A^{1-C-(Y)} \frac{1}{m} + R^{2-A^{3}-COOH}$$

or its reactive derivative at the amino group (VI)

or a salt thereof

(Ia)

or a salt thereof

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or its reactive derivative at the carboxy group or a salt thereof

(VII)

(Ic)

or a salt thereof

Process 4

or its reactive derivative

or its reactive derivative at the carboxy group or a salt thereof

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(IV)

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(3

(A²) соон

Process 2

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at the amino group or a salt thereof

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elimination reaction

of amino protective

drozb

or a sait thereof (Id)

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or a salt thereof

(TP)

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or a salt thereof (Ie)

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Process 5

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Process 7

elimination reaction

of carboxy protective

group

or a salt thereof (If)

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or a salt thereof

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Process 6

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protecting reaction

of amino

(Ie)

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or its reactive derivative at. the amino group

or a salt thereof ...

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or a salt thereof (Id)

protecting reaction of carboxy -2-A³-COOH

(1g)

or its reactive derivative

at the carboxy group

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or a salt thereof

(If)

or a salt thereof

Process 8

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:: :elimination reaction · of amino protective dnoxis

ĸ,

or a salt thereof

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$$R^{1-(x)}_{\ell} + A^{1-c-(x)}_{m} + A^{2}_{m} + A^{2-2-A}_{D} + A^{2}_{D}$$

or a salt thereof

Process 9

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acylation reaction of amino

(II)

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or its reactive derivative

at the amino group

or a salt thereof

$$R^{1-(K)} + A^{1-C-(Y)} + A^{1-C-(Y)} + A^{2} + A^{3} + A^{3$$

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. (ul)

or a salt thereof

1, m and n are each as defined above wherein R^1 , R^2 , R^3 , A^1 , A^2 , A^3 , $\left(\begin{array}{c} \end{array}\right)$

protective group, which may have one or R1 is N-containing cycloalkyl having amino more suitable substituent(s),

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have one or more suitable substituent(s), R_{b}^{1} is N-containing cycloalkyl which may

 $R_{\rm d}^2$ is protected carboxy, $A_{\rm d}^3$ is lower alkylene having protected amino, and

Ag is lower alkylene having amino, Ag is acylamino.

The starting compound (IV) or a salt thereof is novel and can be prepared by the following schemes.

S

 $R^{1}-(x)_{\rho}-A^{1}-COOH$ 10

or its reactive derivative at the carboxy group

or a salt thereof

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at the amino group or a salt thereof

or its reactive derivative

(VIII)

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(IX)

or a salt thereof

Process B

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of carboxy protective elimination reaction group

(XI)

or a salt thereof

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(IV)

or a salt thereof

wherein $R^1,\ A^1,\ A^2,\ -N$ \longrightarrow , X, ℓ and n are each as R⁵ is protected carboxy. defined above, and

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The starting compound (v) or a salt thereof is novel and can be prepared by the following schemes.

Process C

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(2)

<u>۾</u>

(4)

or a salt thereof (Va)

9)

Process D

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15 wittig reaction
$$(7)$$
 $(R6)_3$ $C-(R^8)_4$ (9) (9) (9)

acid/R¹¹⁻OH $[(R^9)_3-Si]_2NLi$

or a salt thereof (Vb)

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A4 is lower alkynylene, wherein

Three R^6 are independently lower alkyl,

R7 is lower alkyl,

Three R^9 are independently lower alkyl, and Two \mathbb{R}^8 are independently halogen,

R¹¹ is lower alkyl.

Among the starting compounds (II), (III), (IV), (VI), (VII), (VIII), and (IX), there are novel compounds. conventional manner in this field of the art or the They can be prepared from the known compounds in a

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similar manners to those disclosed in <u>Preparations</u> and/or

Examples mentioned later in the present specification.

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Thosphate, etc.], a salt with an amino acid [e.g. arginine dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, object compound (I) are conventional non-toxic salts and sodium salt, potassium salt, etc.] and an alkaline earth ammonium salt, an organic base salt [e.g. trimethylamine metal salt [e.g..calcium salt, magnesium salt, etc.] an include a metal salt such as an alkali metal salt [e.g. salt, aspartic acid salt, glutamic acid salt, etc.] and Suitable pharmaceutically acceptable salts of the salt, triethylamine salt, pyridine salt, picoline salt methanesulfonate/benzenesulfonate, toluenesulfonate, etc.], 'an organic acid addition-salte-ferg. formate, hydrochloride, hydrobromide, hydroiodide, sulfate, acetato, trifluoroacetate, maleate, tartrate, etc.], an inorganic acid addition salt [e.g. the like.

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In the above and subsequent descriptions of this definitions are explained in detail as follows : specification, suitable examples of the various

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

term "one or more suitable substituent(s)" may be 1 to 4. The preferable number of the "one or more" in the

Suitable "lower alkyl" may be straight or branched isobutyl, sec-butyl, t-butyl, pentyl, hexyl or the like. ones such as methyl, ethyl, isopropyl, propyl, butyl,

butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester, isopropyl ester, butyl ester, isobutyl ester, tertlower alkyl ester [e.g. methyl ester, ethyl ester, propyl protecting group such as an esterified carboxy group, or ester, etc.] which may have suitable substituent(s), for Suitable "protected carboxy" may be a conventional the like, and concrete examples of the ester moiety in said esterified carboxy group may be the ones such as example, lower alkanoyloxy(lower)alkyl ester [e.g. butyryloxymethyl ester, valeryloxymethyl ester, acetoxymethyl ester, propionyloxymethyl ester, pivaloyloxymethyl ester,

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alkanesulforvi(lower)alkyl ester [e.g. 2-mesylethyl ester, piyaloyloxyethyl ester, 2-propionyloxyethyl ester, 1-acetoxyethyl ester, 1-propionyloxyethyl ester, hexanoyloxymethyl ester, etc.], lower-

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ester, decyl ester, undecyl ester, dodecyl ester, tridecyl octadecyl ester, nonadecyl ester, 3,5-dimethyloctyl ester, 3,7-dimethyloctyl ester, nonyl etc.] or mono(or di or tri)halo(lower)alkyl ester [e.g. 2-indoethyl ester, 2,2,2-trichloroethyl ester, etc.]; ester, tetradecyl ester, pentadecyl ester, hexadecyl higher alkyl ester [e.g. heptyl ester, octyl ester, ester, heptadecyl ester, adamantyl ester, etc.];

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lower alkenyl ester [e.g. (C2-C6)alkenyl sster (e.g. vinyl ester, allyl ester, etc.)];

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lower alkynyl ester [e.g. (C2-C6)alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.)};

alkyl, phenyl, or halo(lower)alkyl, (e.g. benzyl ester, 4ar(lower)alkyl ester which may have one or more suitable methoxybenzyl ester, 4-chlorobenzyl ester, 4-nitrobenzyl nave 1 to 4 lower alkoxy, halogen; nitro, hydroxy, lower substituent(s) [e:g. phenyl(lower)alkyl ester which may ester, phenethyl ester, trityl ester, benzhydryl ester, ois(methoxyphenyl)methyl ester,

chlorophenyl ester, tolyl ester, 4-tert-butylphenyl ester, outylbenzyl ester, 4-trifluoromethylbenzyl ester, etc.)]; substituent(s) [e.g. phenyl ester which may have 1 to 4 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tertaryl ester which may have one or more suitable ower alkyl, or halogen, (e.g. phenyl ester, 4-

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cycloalkyloxycarbonyloxy(lower)alkyl ester which may have lower alkyl (e.g., cyclopentyloxycarbonyloxymethyl ester, -methylcyclohexyloxycarbonyloxymethyl ester, 'i-(or 2-)-[cyclopentyloxycarbonyloxy]ethyl ester, 1-(or 2-)-[cyclohexyloxycarbonyloxy]ethyl.ester, 1=(or:24)= cycloheptyloxycarbonyloxymethyl ester, syclohexyloxycarbonyloxymethyl.ester,

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ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-. ; ;,3..dioxol-4-yl)methyl ester, 1-(or 2-)(5-methy-2-oxo-1,3-(5-(lower)alkyl-2-oxo+1;3+dioxol-4-yl)(lower)alkyl ester lower alkanoyloxy(lower)alkyl ester, ar(lower)alkyl ester [e.g., (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-.. dioxo!-1-yl)ethyl ester, 1-(or.2-)(5-propyl-2-oxo-1,3-dioxol-4-y1) α thyl ester, 1-(or 2-)(5-ethyl-2-oxo-1,3in which the preferred one may be lower alkyl ester, dioxol-4-yl)ethyl ester, etc.]; or the like, 30

lower alkyl, higher alkyl ester, and [5-(lower)alkyl-2oxo-1,3-dioxol-4-yl](lower)alkyl ester;

cyclohexyloxycarbonyloxy)ethyl ester and pivaloyloxymethyl chlorobenzyl ester, adamantyl ester, (5-methyl-2-oxo-1,3ester, isobutyl ester, butyl ester, pentyl ester, hexyl ester, benzyl ester, 4-trifluoromethylbenzyl ester, 4and the more preferred one may be methyl ester, ethyl dioxol-4-yl)methyl ester, (1Suitable "lower alkanyl-ylidene" may include straight in which the preferred one may be (C1-C4)alkanyl-ylidene; or branched one such as methine, 1-ethany1-2-ylidene, 1propanyl-3-ylidene, 2-methyl-1-propanyl-3-ylidene, 7pentanyl-5-ylidene, l-hexanyl-6-ylidene and the like, and the more preferred one may be methine.

ester.

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C4)alkylene; and the more preferred one may be methylene methylmethylene, 1-ethylethylene, 2-ethylpropylene, and oranched one such as methylene, ethylene, trimethylene, Suitable "lower alkylene" may include straight or the like, in which the preferred one may be $(C_{1}$ tetramethylene, pentamethylene, hexamethylene, ethylene and trimethylene.

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Suitable "lower alkenylene" may include straight or ethylvinylen, 1 or 2 or 3-methylpropenylene, 1 or 2 or 3-pentenylene, 1 or 2 or 3-hexenylene, methylvinylene, branched one having 2 to 6 carbon atom(s) ... such as 3-ethylpropenylene, 1 or 2 or 4-methyl-1 or vinylene, propenylene, butenylene, 1 or 2 or 2-butenylene, or the like.

group as explacad below, a conventional protecting group ... Suitable "amino protective group" may include acyi such as ar(low: , alkyl which may have 1 to 3 suitable substituent(s) (e.g. benzyl, phenethyl,

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l-phenylethyl, benzhydryl, trityl, etc.), {5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl](wer)alkyl [e.g. (5-methyl-2-oxo-

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cycloalkyloxycarbonyloxy(lowsr)alkyl ester which may have

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which may have one or more suitable substituent(s),

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carbonic acid, carbamic acid, sulfonic acid, and the like. heterocyclic-aliphatic acyl derived from carboxylic acid, 1,3-dioxol-4-y1)methyl, etc.] or the like; and the like. aliphatic acyl, aromatic acyl, arylaliphatic acyl and Suitable "acyl group" and "acyl" may include

Suitable example of said "acyl group" may be illustrated as follows.

pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, Aliphatic acyl such as lower or higher alkanoyl 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, (e.g., formyl, acetyl, propancyl, butancyl, nonadecanoyl, icosanoyl, etc.);

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lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);

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lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);

lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.); or the like;

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Aromatic acyl such as

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aroyl (e.g.; benzoyls toluoyl, naphthoyl, etc.); phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), ar(lower)alkanoyl: [e.g., phenyl(C1-C5)alkanoyl (e.g., C6)alkenoyl (e.g., naphthylpropencyl, naphthylbutencyl, ar(lower)alkenoyl [e.g., phenyl(C3-C6)alkenoyl (e.g., Phenylpropencyl, phenylbutencyl, phenylmethacrylcyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(C3as naphthylpropancyl, naphthylbutancyl, etc.]; naphthyl(Cl=C6)alkanoyl (e.g:)#naphthylacetyl, phenylacetyl, phenylpropanoyl, phenylbutanoyl, etc.), etc.];

C6)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), etc.]; ar(lower)alkoxycarbonyl [a.g., phenyl(Cl-

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arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.); arylcarbamoyl (e.g., phenylcarbamoyl, etc.); aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, aryloxycarbonyl (e.g., phenoxycarbonyl, arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthyloxycarbonyl, etc.); naphthylglyoxyloyl, etc.); phenoxypropionyl, etc.);

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heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, arylsulfonyl which may have 1 to 4 lower alkyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like; heterocyclicpentanoyl, heterocyclichexanoyl, etc.); heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, Heterocyclic acyl such as heterocyclichexenoyl, etc.); heterocycliccarbonyl;

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heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" unsaturated monocyclic or polycyclic heterocyclic group as mentioned abov means, in more detail, saturated or 25 containing at least one hetero-atom such as an oxygen, in which suitable "heterocyclic moiety" in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkyl", heterocyclicglyoxyloyl; or the like; sulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be heterocyclic group such as

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imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), unsaturated 3 to 8-membered (more preferably 5 or tetrazo] 1 (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s); for example, pyrrolyl, pyrrolinyl, PYCE .nyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-

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aturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 imidazolidinyl, piperidyl, piperazinyl, etc.; nitrogen atom(s), for example, pyrrolidinyl,

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unsaturated condensed heterocyclic group containing l to 4 nitrogen atom(s), for example, indolyl, isoindolyl, dihydroquinolyl, isoquinolyl, indazolyl, quinoxalinyl, indolinyl, indolizinyl, benzimidazolyl, guinolyl, dihydroquinoxalinyl, benzotriazolyl, etc.;

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oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, g 6-membered) heteromonocyclic group containing 1 to 2 unsaturated 3 to 8-membered (more preferably 5 oxazolyl, isoxazolyl, oxadiazolyl (e.g., etc), etc.;

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oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 morpholinyl, sydnonyl, etc.;

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unsaturated condensed heterocyclic group containing 1 . unsaturated 3 to 8 membered (more preferably 5 or to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-1,2,5-thiadiazolyl; etc.), dihydrothlazinyl, etc.;

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sulfur atom(s) and 1 to 3 nitrogen_atom(s), for example, saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 thiazolidinyl, etc.;

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unsaturated 3 to 8-membered (more preferably 5 or 6membered) heteromonocyclic group containing 1 to 2 sulfur

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atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.; unsaturated condensed heterocyclic group containing to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiażolyl, benzothiadiazolyl, etc.;

6-membered) heteromonocyclic group containing an oxygen unsaturated 3 to 8-membered (more preferably 5 or atom, for example, furyl, etc.;

6-membered) heteromonocyclic group containing an oxygen unsaturated 3 to 8-membered (more preferably 5 or atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

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unsaturated condensed heterocyclic group containing to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

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unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

The acyl moiety as mentioned above may have one to ten, same or different, suitable substituent(s) such as lower alkoxy (e.g., methoxy, ethoxy, propoxy, etc.); lower alkylthio (e.g., methylthio, ethylthio, etc.); lower,alkylaminof(e.g., methylamino, ethylamino, lower alkyl (e.g., methyl, ethyl, propyl, etc.); propylamino, etc.);

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...cyclo(lower)alkyl [e.g. cyclo(C3-C6)alkyl (e.g., cyclopentyl, cyclohexyl, etc.]);

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cyclo(lower)alkenyl [e.g cyclo(C3-C6)alkenyl (e.g., cyclohexenyl, cyclohexadienyl; etc);

amino; amino protective group as mentioned above; hydroxy; halogen (e.g., fluorine, Larine, bromine, iodine); carboxy; protected carboxy as mentioned above; sulfo; protected hydroxy as mentioned below; cyano; nitro; sulfamoyl; imino; oxo;

amino(lower)alkyl (e.g., aminomethyl, aminoethyl, etc.);

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mentioned above, phenyl(lower)alkyl which may have one or t-butyldimethylsilyl, etc.), etc.], tetrahydropyranyl and Suitable "protected hydroxy" may include acyl as 4-methoxybenzyl, trityl, etc.), trisubstituted silyl [e.g., tri(lower)alkylsilyl (e.g., trimethylsilyl, more suitable substituent(s) (e.g., benzyl, the like.

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ar(lower)alkoxycarbonyl and the most preferred one may be The more preferred example of "amino protective group" may be lower alkoxycarbonyl or t-butoxycarbonyl or benzyloxycarbonyl

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Suitable "lower alkylene" in the term "lower alkylene which may have one or more suitable substituent(s)" can be referred to the ones as exemplified above.

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lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, t-butaxy, pentyloxy, neopentyloxy, t-pentyloxy; Suitable example of "suitable substituent(s)" in the term "lower alkylene which may have one or more suitable substituent(s)" may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, neopentyl, t-pentyl, hexyl, etc.); hexyloxy, etc.);

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propenyl, allyl, 1-methylallyl, 1 cr 2 or 3-butenyl, 1 or lower alkenyl [e.g. (C2-C6)alkenyl (e.g., vinyl, 1-2 or 3 or 4 pentenyl; Nor, 2 or 3 or 4 or 5-hexenyl, THE . etc.).];

1 or 2 or 3-butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or propynyl, propargyl, 1-methylpropargyl, 1-ethylpropargyl, lower alkynyl [e.g. (C2-C6)alkynyl (e.g., ethynyl, 1-3 or 4 or 5 hexynyl, etc.);

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mono(or di or tri)halo(lower)alkyl (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl;

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dichloromethyl, trichloromethyl; bromomethyl, dibromomethyl, tribromomethyl, 1 or

2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, etc.);

carboxy; protected carboxy as mentioned above; hydroxy; halogen (e.g., chlorine, bromine, fluorine, iodine); protected hydroxy as mentioned above;

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aryl (e.g., phenyl, naphthyl, etc.);

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atom(s) (e.g. indolyl, isoindolyl, indolynyl, indolizinyl, heterocyclic group as mentioned above [e.g. unsaturated condensed heterocyclic group containing 1 to 4 nitrogen benzimidazolyl, quinolyl, dihydroguinolyl, isoguinolyl, indazolyl, quinoxalinyl, dihydroquinoxalinyl, benzotriazolyl, etc.)];

ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.);

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such as ar(lower)alkyl having one or more (preferably 1 to ar(lower) alkyl having one or more suitable substituent(s) 4) lower alkoxy, halogen, cyano, halo(lower)alkyl, lower alkylene dioxy or the like;

carboxy(lower)alkyl; protected carboxy(lower)alkyl; nitro; amino;

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protected amino, i.e. amino protected by aforesaid "amino

formylamino, acetylamino, propanoylamino, butanoylamino, protective group", preferably, acylamino, in which acyl moiety can be aforementioned "acyl"; such as aliphatic acylamino such as lower or higher alkanoylamino (e.g., 2-méthylpropanoylamino, pentanoylamino, 2,2-

tetradecancy. Lamino, pentadecanoy lamino, hexadecanoy lamino, heptadecanoylamino, octadecancylamino, nonadecanoylamino, dimethylpropanoylamino, hexanoylamino, heptanoylamino, icosanoylamino, etc.), cyclo(lower)alkylcarbonylamino undecanoylanino, dodecanoylamino, tridecanoylamino, octanoylamino, nonanoylamino, decanoylamino, [e.g. cyclo(C3-C6)allylcarbonylamino (e.g.

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cyclopentylcarbonylamino, cyclohexylcarbonylamino, etc.)], 2- or ethoxypropionylamino, etc.), lower alkynylcarbonylamino alkoxy(lower)alkanoylamino (e.g. methoxyacetylamino, -methoxypropionylamino, ethoxyacetylamino, 2- or 3lower or higher alkoxysulfonylamino (e.g., methoxycyclopropylcarbonylamino, cyclobutylcarbonylamino, n-pentylsulfonylamino, neo-pentylsulfonylamino, t-butoxycarbonylamino, pentyloxycarbonylamino, 3sec-butylsulfonylamino, t-butylsulfonylamino, .-methylpropargylcarbonylamino, 1- or 2- or methoxycarbonylamino, ethoxycarbonylamino, propylsulfonylamino, n-butylsulfonylamino, lower or higher alkoxycarbonylamino (e.g., lower or higher alkylsulfonylamino (e.g., nethylsulfonylamino, ethylsulfonylamino, e.g. (C2-C6)alkynylcarbonylamino (e.g. heptyloxycarbonylamino, etc.), lower butynylcarbonylamino, etc.), hexylsulfonylamino, etc.), propargylcarbonylamino,

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aroylamino which may have one or more (preferably 1 to 3) suitable substituent(s) (e.g. benzoylamino, toluoylamino, ö ar(lower)alkanoylamino [e.g., pheny1(C1-C6)alkanoylamino naphthyl(lower)alkanoylamino (e.g., naphthylacetylamino, naphthylpropanoylamino, naphthylbutanoylamino, etc.), Second philosylamino, 2- or 3- or 4-hydroxybenzoylamino, 2chenylpentanoylamino, phenylhexanoylamino, etc.), 🗁 (e.g., phenylacetylamino, phenylpropanoylamino, chlorobenzoylamino, phenylbenzoylamino, etc.), phenylbutanoylamino, phenylisobutanoylamino, 3- or 4-methoxybenzoylamine, 2- or 3- or 4sulfonylamino, ethoxysulfonylamino, etc.),

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sr(lower)alkenoylamino [e.g., phenyl(C3-C6)alkenoylamino (e.g., phenylpropencylamino, phenylbutencylamino,

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phenylhexenoylamino, etc.), naphthyl(C3-C6)alkenoylamino (e.g., naphthylpropencylamino, naphthylbutencylamino, phenylmethacryloylamino, phenylpentenoylamino, etc.), etc.],

ar(lower)alkoxycarbbnylamino [e.g., phenyl(C1-C6)alkoxycarbonylamino (e.g. benzyloxycarbonylamino,

aryloxycarbonylamino (e.g., phenoxycarbonylamino, phenethyloxycarbonylamino, etc.), etc.], naphthyloxycarbonylamino, etc.),

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erylthiocarbamoylamino (e.g., phenylthiocarbamoylamino, arylcarbamoylamino (e.g., phenylcarbamoylamino, etc.), aryloxy(lower)alkanoylamino (e.g., phenoxyacetylamino, ohenoxypropionylamino, etc.), etc.),

arylglyoxyloylamino (e.g., phenylglyoxyloylamino, arylsulfonylamino (e.g. phenylsulfonylamino, pcolylsulfonylamino, etc.), or the like; naphthylglyoxyloylamino, etc.),

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diisopropylamino, ethylmethylamino, isopropylmethylamino, hydroxy(lower)alkyl; protected hydroxy(lower)alkyl; acyl di(lower)alkylamino (e.g., dimethylamino, diethylamino, ethylmethylamino, ethylpropylamino, etc.); as mentioned above; cyano; mercapto; oxo;

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butylthiomethyl, methylthioethyl, ethylthioethyl, etc.); ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, lower alkylthio(lower)aligyl. (e.g. methylthiomethyl, arylthic lower alkyl (e.g. phenylthiomethyl, phenylthioethyl, etc.);

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. Elasulforyl(lower)alkyl (e.g. phenylsulfonylmethyl, الابائينية بالباهيرية المالية ا methylsulfonylmethyl, ethylsulfonylmethyl, ..lower alkylsulfonyl(lower)alkyl (e.g. .olylsulfonylethyl, e.c.); 3

propylsulfonylmethyl, etc.);

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aforementioned "acyl" [e.g., arylsulfonylamino(lower)alkyl phenylsulfonylaminoethyl, p-tolylsulfonylaminomethyl, acylamino(lower)alkyl, in which acyl moiety can be (e.g., phenylsulfonylaminomethyl, p-tolylsulfonylethyl, etc.),

methylsulfonylaminomethyl, ethylsulfonylaminomethyl, lower alkylsulfonylamino(lower)alkyl (e.g., propylsulfonylaminomethyl,

butylsulfonylaminomethyl, t-butylsulfonylaminomethyl, pentylsulfonylaminoethyl, etc.), etc.];

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methylcarbonylmethyl, ethylcarbonylmethyl, lower alkylcarbonyl(lower)alkyl (e.g. propylcarbonylmethyl, etc.); aroyl(lower)alkyl (e.g. benzoylmethyl, naphthoylmethyl, heterocyclic(lower)alkyl such as (lower)alkyl having toluoylmethyl, anisoylmethyl, etc.); 12

heterocyclic group as exemplified above [e.g. (C1-C6)alkyl having unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s) (e.g. indolylethyl,

dihydroquinolylmethyl, isoquinolylethyl, indazolylethyl, isoindolylethyl, indolyinylmethyl, indolizinylethyl, quinoxalinylethyla, dihydroquinoxalinylmethyl, benzimidazolylmethyl, quinolylethyl, benzotriazolylethyl, etc.)]; . 20

n-propylsulfamoylmethyl, isopropylsulfamoylmethyl, n-butylsulfamoylmethyl, t-butylsulfamoylmethyl, and the second of the second o 25 months alkyl sulfamoyl(lower)alkyl (e.g. methylsulfamoylethyl, etc.); arylsulfamoyl(lower)alkyl (e.g. phenylsulfamoylmethyl, methylcarbamoylmethyl, ethylcarbamoylmethyl, tolylsulfamoylmethyl, phenylsulfamoylethyl, lower alkylcarbamoyl(lower)alkyl (e.g. naphthylsulfamoylmethyl, etc.); 30

r-propylcarbamoylmethyl, isopropylcarbamoylmethyl,

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n-butylcarbamoylmethyl, t-butyłcarbamoylmethyl, methylcarbamoylethyl, etc.); arylcarbamoyl(lower)alkyl (e.g. phenylcarbamoylmethyl, tolylcarbamoylmethyl, phenylcarbamoylethyl,

naphthylcarbamoylmëthyl, etc.);

methoxyphenethylcarbamoyl, 3-methoxyphenethylcarbamoyl, 4suitable substituent(s) [e.g. phenyl(C1-C6)alkylcarbamoyl ar(lower)alkylcarbamoyl which may have one or more methoxyphenethylcarbamoyl, etc.) and the like, which may have 1 to 3 lower alkoxy (e.g. 2-

in which the more preferred one may be (C1-C6)alkyl; (C2unsaturated condensed heterocyclic group containing 1 to 4 phenyl(C1-C6)alkyl having 1 to 4 (C1-C6)alkoxy, halo(C1aroylamino which may have 1 to 3 hydroxy, (C1-C6)alkoxy, C6)alkenyl; (C2-C6)alkynyl; phenyl; phenyl(C1-C6)alkyl; halogen or phenyl; cyclo(C3-C6)alkylcarbonylamino; (C1-C6)alkyl or (C1-C6)alkylene dioxy; (C1-C6)alkyl having nitrogen atom(s); cyano; amino; (C1-C6)alkanoylamino;

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and the more preferred one may be methyl, ethyl, vinyl, C6)alkynylcarbonylamino; (C1-C6)alkylsulfonylamino; phenylsulfonylamino; phenyl(C1-C6)alkylcarbamoyl; C6)alkoxy(C1-C6)alkylcarbonylamino; (C2ethynyl, cyano, phenyl, phenthyl,

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4-methoxyp' nethyl, 3,4-dimethoxyphenethyl, 2-methoxyphenethyl, 3-methoxyphenethyl,

3-trifluoromethylphenethyl, 3,4-methylenedioxyphenethyl, phenylsulfonylamino, n-butylsulfonylaminomethyl, 2-indolylethyl, 4-methoxyphenethylcarbamoyl,

benzoylamino, amino, acetylamino, p-hydroxybenzoylamino, 3-methoxypropionylamino, biphenylcarbonylamino and p-methoxybenzoylamino, p-chlorobenzoylamino, n-butanoylamino, cyclopropylcarbonylamino, propargylcarbonylamino.

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Suitable "N-containing heterocyclic group" ary

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include saturated or unsaturated monocyclic or polycyclic heterocyclic group containing at least nitrogen atom and which may also contain the other hetero-atom such as an oxygen, sulfur atom or the like.

And, especially preferable N-containing heterocyclic group may be heterocyclic group such as

imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), unsaturated 3 to 8-membered (more preferably 5 or cetrazolyl (e.g., lH-tetrazolyl, 2H-tetrazolyl, etc.), 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, cyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-

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membered heteromonocyclic group containing 1 to 4 nitrogen saturated 3 to 8-membered (more preferably 5 or 6atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

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unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, quinoxalinylandinydroquinoxalinyl, benzotriazolyl, etc.; teirahydroquinolyl (e.g. 1,2,3,4-tetrahydroquinolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, etq.), dihydroguinolyl, isoguinolyl, indazolyl,

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the conviction atom(s) and 1 to 3 nitrogen atom(s), for example, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxazolyl, isoxazolyl, oxadiazolyl (e.g., etc.), etc.;

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oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonicyclic group containing 1 to 2 morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing

to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

5 or unsaturated 3 to 8-membered (more preferably

sulfur atom(s) and $^{!}\mathtt{l}$ to $\mathtt{3}$ nitrogen atom(s), for example, chiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 6-membered) heteromonocyclic group containing 1 to 2 chiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

6-membered heteromonocyclic group containing 1 to 2 sulfur saturated 3 to 8-membered (more preferably 5 or atom(s) and 1 to 3 nitrogen atom(s), for example, thiomorpholinyl, thiazolidinyl, etc.;

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unsaturated condensed heterocyclic group containing 1 example, benzothiazolyl, benzothiadiazolyl, etc. and the to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for

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nembered heteromonocyclic group containg 1 to 4 nitrogen containing 1 to 4 nitrogen atom(s), or saturated 5 or 6membered heteromonocyclic group containing 1 to 2 oxygen in which the preferred one may be saturated 5 or 6atom(s), unsaturated condensed heterocyclic group and the more preferred one may be piperidyl, atom(s) and 1 to 3 nitrogen atom(s);

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"xrolidinyl, morpholinyl and (1,2;3;4-tetrahydroguinolyl.

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Suitable "N-containing cyclo(lower)alkyl" in the term example, azetidinyl, pyrrolidinyl, piperidyl, pipetzzinyl, 'N-containing cyclo(lower)alkyl which may have one or suitable substituent(s)" may include 3 to 8-membered cycloalkyl containing 1 to 3 nitrogen atom(s), for

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'N-containing cyclo(lower)alkyl which may have one or more suitable substituent(s)". may include oxc. amino protective Suitable "suitable substituent(s)" in the term group as mentioned above

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of which may have one or more suitable substituent(s)" may Suitable "suitable substifuent(s)" in the term "lower alkylene, lower alkanyl-ylidene or lower alkenylene each include lower alkyl or oxo.

'N-containing heterocyclic group which may have one or more suitable substituent(s)" may include lower alkyl, Suitable "suitable substituent(s)" in the term phenyl, halogen or oxo.

propynylene, 2- or 3-butynylene, 2- or 3- or 4-pentynylene Suitable "lower alkynylene" may include the ones having 2 to 6 carbon atoms such as ethynylene, 2or 2- or 3- or 4- or 5-hexynylene.

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In the compound (I) as explained above, the preferred one is the following compound (I-A) :

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Compound (I-A):

$$R^{1-(K)} \xrightarrow{\rho} A^{1-C-(Y)} \xrightarrow{N} (A^{2}) \xrightarrow{n} Z^{-A}^{3-R^{2}}$$
 (I-A)

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wherein R1 is 3 to 8 membered cycloalkyl

containing 1 to 3 nitrogen atom(s) which may have one or more suitable substituent(s), \mathbb{R}^2 is carboxy or esterified carboxy,

 $\mathbf{A}_{2,1}^{1}$ is lower alkylene, lower alkanyl-ylidene or

lower alkenylene, each of which may have one or more suitable substituent(s),

 ${\tt A}^3$ is lower alkylene which may have one or more suitable substituent(s), A² is Jower alkylene,

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is a group of the formula:

is saturated 3 to 8 membered condensed heterocyclic group containing 1 to nitrogen atom(s) which may have one or more more suitable substituent(s) or saturated 3 containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have one or more heteromonocyclic group containing 1 to 4 4 nitrogen atom(s) which may have one or suitable substituent(s), unsaturated to 8-membered heteromonocyclic group suitable substituent(s), wherein

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is O, S, or NH,

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$$z is \begin{pmatrix} -c - N - C \\ 1 & 1 \\ 0 & R^3 \end{pmatrix} \begin{pmatrix} N - C \\ 1 & 1 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} -c \\ 1 & 1 \\ 0 & 0 \end{pmatrix}$$

and the more preterred one is the aforementioned compound (wherein \mathbb{R}^3 is hydrogen or lower alkyl), l is an integer of 0 or 1, m is an integer of 0 or 1, n is an integer of 0 or 1,

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wherein \mathtt{R}^1 is piperidyl which may have 1 or 2 oxo or [5-(I-A),

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(lower)alkyl-2-oxo-1,3-dioxol-4-yl]-... (lower) alkyl,

is piperidyl, morpholinyl,

suitable substituent(s) selected from the group co sisting of (C1-C6)alkyl;, (C2tetrahydroguinolyl or pyrrolydinyl, ${\tt A}^3$ is lower alkylene which may have 1 to 3 C6)alkenyik (C2-C6)alkynyl; phenyl;

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C6)alkanoylamino; aroylamino which may have C6)alkylsulfonylamino; phenylsulfonylamino; 1 to 3 hydroxy, (C1-C6)alkoxy, halogen or C6)alkyl or (C1-C6)alkylene dioxy; (C1-(C1-C6)alkoxy(C1-C6)alkylcarbonylamino; phenyl; cyclo(C3-C6)alkylcarbonylamino; phenyl(C1-C6)alkyl; phenyl(C1-C6)alkyl C6)alkyl having unsaturated condensed having 1 to 4 (C1-C6)alkoxy, halo(C1heterocyclic group containing 1 to 4 nitrogen atom(s); cyano; amino; (Cl-(C2-C6)alkynylcarbonylamino; (C1and phenyl(C1-C6)alkylcarbamoyl;

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 R^2 , R^3 , A^1 , A^2 , X, Y or Z are each as defined

l is an integer of 0,

m is an integer of 0,

n is an integer of 0,

and the much more preferred one is the aforementioned compound (I-A),

wherein R^l is piperidyl,

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A3 is lower alkylene which may have lower alkyl, A¹ is lower alkylene or lower alkanyl-ylidene,lower alkynyl or lower alkanoylamino,

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 $R^2,\ R^3,\ L^2,\ Y,\ \ell$, in and n are each as defined in the more preferred one

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and the another much more preferred one is the aformentioned compcund (I+A), wherein R1 is piperidyl, is lower alkylene or lower alkanyl-ylidene,

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 $^{
m A3}$ is lower alkylene which may have lower alkyl, lower alkynyl or lower alkanoylamino,

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is morpholinyl,

 $R^2,\ R^3,\ A^2,\ Y,\ \ell$, m and n are each as defined in the more preferred one.

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In the compound (I) as explained above, another preferred one is the following compound (I-B)

Compound (I-B) 15

$$R^{1} + (x)_{\overline{y}} - A^{1} - C + (x)_{\overline{m}} + (x^{2})_{\overline{m}} - z - A^{3} - R^{2}$$
 (I-B

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wherein \mathbb{R}^1 is N-containing cyclealkyl which may

have one or more suitable substituent(s), \mathbb{R}^2 is carboxy or esterified carboxy,

lower alkenylene; each of which may have one \mathtt{A}^1 is lower alkylene, [cwer alkanyl-ylidene or] or more suitable substituent(s),

A2 is lower alkyl

hanay have one or more A3 is lower alky suitable s

of the formula:

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is N-containing heterocyclic group which may have one or more suitable substituent(s), wherein

X is O,

is NH,

is
$$(-N-)$$
 $(N-C)$ $(-C-)$

(wherein R³ is hydrogen or lower alkyl),

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{ is an integer of 1,

m is an integer of 0 or 1,

n is an integer of 0 or 1,

and the more preferred one is the aforementioned compound (I-B),

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wherein \mathtt{R}^1 is piperidyl, piperazinyl or azetidinyl, each (lower)alkyl-2-oxo-1,3-dioxol-4-yl]of which may have 1 or 2 oxo or [5-

(lower)alkyl,

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tetrahydroquinolyl or pyrrolydinyl, is piperidyl, morpholinyl,

suitable substituent(s) selected from the C6)alkyl or (C1-C6)alkylene dioxy; (C1group consisting of (C1-C6)alkyl; (C2phenyl (C1-C6)alkyl; phenyl (C1-C6)alkyl C6)alkyl having unsaturated condensed naving 1 to 4 (C1-C6)alkoxy, halo(C1-A³ is lower alkylene which may have 1 to 3 neterocyclic group containing 1 to 4 C6)alkenyl; (C2-C6)alkynyl; phenyl;

nitrogen atom(s); cyano; amino; (C1-30

C6)alkoxy(C1-C6)alkylcarbonylamino; (C2-C6)alkynylcarbonylamino; (C1-

C6)alkysulfonylamino; phenylsulfonylamino; and phenyl(C1-C6)alkylcarbamoyl;

R², R³, A¹, A², X, Y, Z or ! are each as

defined above,

m is an integer of 0,

n is an integer of 0,

and the much more preferred one is the aforementioned compound (I-B),

wherein R¹ is piperidyl,

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A¹ is lower alkylene,

 ${\tt A}^3$ is lower alkylene which may have lower alkyl, lower alkynyl or lower alkanoylamino,

is piperidyl,

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 $\rm R^2,~R^3,~A^2,~X,~Y,~\ell$, m and n are each as defined in the more preferred one,

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and the much more preferred one is the aforementioned compound (I-B)

- wherein R1 is piperidyl,

Al is lower alkylene,

 ${\tt A}^3$ is lower alkylene which may have lower alkyl,

lower alkynyl or lower alkanoylamino,

 $R^2,\ E^3,\ A^2,\ X,\ Y,\ \ell$, m and n are each as defined in the more preferred one.

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have 1 to 3 hydroxy, (C1-C6)alkoxy, halogen

C6)alkanoylamino; aroylamino which may

or phenyl; cyclo(C3-C6)alkanoylamino; (C1-

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In the compound (I) as explained above, another preferred one is the following compound (I-C) Compound (I-C) :

$$R^{1} - (x) + A^{1} - C - (x) + A^{2} + A^{2} - A^{3} - R^{2}$$
 (I-C)

piperidyl which may have 1 or 2 oxo or [5-[lower]alkyl-2-oxo-1,3-dioxol-4-yl]wherein R^l is

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(lower)alkyl;

 \mathtt{a}^1 is lower alkanyl-ÿlidene or lower alkenylene, \mathbb{R}^2 is carboxy or esterified carboxy,

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A³ is lower alkylene which may have lower alkyl, lower alkynyl or lower alkanoylamino, A² is lower alkylene,

is a group of the formula:

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. is piperidyl; morpholinyl, tetrahydroquinolyl or pyrrolydinyl, wherein

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W is PH,

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(wherin R3 is hydrogen),

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is 0,

is an integer of 0 or 1,

is an integer of 0 or 1,

and the other preferred one is the aforementioned compound (I-C)

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wherein A3 is lower alkylene häving lower alkynyl or lower alkanoylamino,

R1, R2, R3, A1, A2, X, Y, Z, and & are is piperidyl or morpholinyl,

m is an integer of 0,

each as defined above.

n is an integer of 0.

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The processes for preparing the object compound (I) of the present invention are explained in detail in the following

Process 1

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derivative at the carboxy group or a salt thereof with a þe compound (III) or its reactive derivative at the amino prepared by reacting a compound (II) or its reactive The object compound (Ia) or a salt thereof can group or a salt thereof.

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anhydride; an activated amide; an activated ester, and the be an acid chioride; an acid azide; a mixed acid anhydride sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic embassilic acid [e.g. acetic acid; propionic acid, butyric Suitable reactive derivative at the carboxy group of like. Suitable examples of the reactive derivatives may isopentanoic acid, 2-ethylbutyric acid, trichloroacetic anid; sulfurous acid, thiosulfuric acid, sulfuric acid, with an acid such as substituted phosphoric acid [e.g. halocenated phosphoric acid, etc.], dialkylphosphorous the compound (II) may include an acid halide, an acid acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid; asobutyric acid, pivalic acid, pentanoic acid, diphenylyhosphoric acid, dibenzylphosphoric acid, dialkylphosphoric acid, phenylphosphoric acid,

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acid, etc.]; a symmetrical acid anhydride; an activated dimethylpyrazole, triazole, tetrazole or 1-hydroxy-lHbenzotriazole; or an activated ester [e.g. cyanomethyl [(CH3)2N=C-] ester, vinyl ester, propargyl ester, ester, methoxymethÿl ester, dimethyliminomethyl amide with imidazole, 4-substituted imidazole, p-nitrophenyl ester,

phenylazophenyl ester, phenyl thioester, p-nitrophenyl 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester,

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pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl reactive derivative can optionally be selected from them 1-hydroxy-1H-benzotriazole, etc.], and the like. These thioester, etc.], or an ester with a N-hydroxy compound thioester, p-cresyl thioester, carboxymethyl thioester, according to the kind of the compound (II) to be used. pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-

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Suitable salts of the compound (II) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

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the like; a derivative formed by reaction of the compound: the compound (III) may include Schiff's base type amino or aldehyde, ketone or the like; a silyl derivative formed by and the stantomeric enamine type isomer formed; by the reaction mono(trimethylsilyl)acetamide, bis trimethylsilyl)urea or the reaction of the compound (III) with a silyl compound Suitable reactive derivative at the amine group of of the compound (III) with a carbonyl compound such as (III) with phosphorus trichloride or phosgene, and the such as bis(trimethylsilyl)acetamide,

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Suitable salts of the compound (III) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

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the reaction. These conventional solvent may also be used The reaction is usually carried out in a conventional other organic solvent which does not adversely influence solvent such as water, alcohol [e.g. methanol, ethanol, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N2dimethylformamide, pyridine or any etc.], acetone, dioxane, acetonitrile, chloroform, in a mixture with water.

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In this reaction, when the compound (II) in used in a thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. Pethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-eth/1-7-hydroxybenzisoxazolium salt; oxychloride (phosphory's chloride); phosphorus trichloride; preferable carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N, N'-diethylcarbodiimide, N, N'-diisopropylcarbodiimide; polyphosphate; isopropyl polyphosphate; phosphorous 1-alkoxy-1-chloroethylene; trialkylphosphite; ethyl diphenylketene-N-cyclohexylimine; ethoxyacetylene; free acid form or its salt form, the reaction is N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide N-cyclohexyl-N'-morpholinoethylcarbodiimide; pentamethyleneketene-N-cyclohexylimine; N, N'-carbonylbis-(2-methylimidazole);

carbonate, alkali metal bicarbonate, tri(lower)alkylamine, The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal

"....yl chloride, phosgene, trichloromethyl chloroformate;

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prepared by the reaction of N,N-dimethylformamide with

intramolecular_salt; 1-(p-chlorobenzenesulfonyloxy)-6-

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chloro-_H-benzvtriazole; so-called Vilsmeier reagent

paiosphorus oxychloride, methanesulfonyl chloride, etc.;

or the like.

N,N-di(lower)alkylbenzylamine, or the like. pyridine, N-(lower)alkylmorpholine,

reaction is usually carried out under cooling to warming. The reaction temperature is not critical, and the

Process 2

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compound (V) or its reactive derivative at the amino group derivative at the carboxy group or a salt thereof with a The object compound (Ib) or a salt thereof can be prepared by reacting a compound (IV) or its reactive or a salt thereof.

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to that of Process 1 mentioned in the above, and therefore This reaction can be carried out in a similar manner the reaction mode and reaction conditions [e.g. reactive derivative, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in

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Process 3

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derivative at the carboxy group or a salt thereof with a The object compound (Ic) or a salt thereof can be prepared by reacting a compound (VII) or its reactive compound (VI) or its reactive derivative at the amino San Sangroup, or asalt thereof.

to that of Process 1 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. reactive derivative, solvent, reaction temperature tete. of this reaction are to be referred to those as explained in Process 1.

Process 4

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prepared by subjecting a compound (Id) or a salt thereof The object compound (Ie) or a salt thereof can be to elimination reaction of amino protective group.

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conventional method such as hydrolysis, reduction or the This reaction is carried out in accordance with a

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The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

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Potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, thereof, trialkylamine [e.g. trímethylamine,

1,5-diazabicyclo[4.3.0]non-5-ene, triethylamine, etc.], picoline, 1,4-diazabicyclo[2.2.2]octane,

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1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

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formic acid, acetic acid, propionic acid, trichloroacetic e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, acid, trifluoroacetic acid, etc.) and an inorganic acid Suitable acid may include an organic acid [e.g. hydrogen chloride, hydrogen bromide, etc.].

trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, e.g. anisole, phenol, atc.j.

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The reaction s usually carried out in a solvent such The reaction temperature is not critical and the methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the reaction is usually carried out under cooling to warming. as water, an alcohol [e.g. methanol, etc.], solvent.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical

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trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid reduction are a combination of metal [e.g. tin, zinc, [e.g. formic acid, acetic acid, propionic acid, acid, hydrobromic acid, etc.].

platinum plate, spongy platinum, platinum black, colloidal reduced copper, Raney copper, Ullman copper, etc.] and the palladium oxide, palladium on carbon, colloidal palladium, platinum, platinum oxide, platinum wire, etc.], palladium Suitable catalysts to be used in catalytic reduction nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. carbonate, etc.], nickel catalysts [e.g. reduced nickel, reduced iron, Raney iron, etc.], copper catalysts [e.g. conventional ones such as platinum catalysts [e.g. catalysts [e.g. spongy palladium, palladium black, palladium on barium, sulfate, palladium on barium like.

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Additionally singusesthat the above-mentioned acids to be usediinnichemical reduction are in liquid, they can also be sused sas a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, the reaction such as water, methanol, ethanol, propanol, conventional solvent which does not adversely influence and other conventional solvent such as diethyl ether, N,N-dimethylformamide)montacumixture thereof. The reduction is usually carried out in a

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critical and the reaction is usually carried out under The reaction temperature of this reduction is not diomane, tetrahydrofuran, etc., or a mixture thereof. cooling to warming.

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The present invention includes within the scope of the invention the case that protected carboxy in \mathbb{R}^2 is transformed into carboxy.

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Process 5

prepared by subjecting a compound (If) or a salt thereof to elimination reaction of the carboxy protective group. The object compound (Ig) or a salt thereof can be

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to that of Process 4 mentioned in the above, and therefore This reaction can be carried out in a similar manner this reaction are to be referred to those as explained in acid, catalyst, solvent, reaction temperature, etc.] of the reaction mode and reaction conditions [e.g. base, Process 4.

Process 6

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prepared by reacting the compound (Ie) or a salt thereof The object compound (Id) or a salt thereof can be to protecting reaction of amino.

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conventional manner such as the one described in Examples This reaction can be carried out according to a or the similar manners thereto.

Process 7

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prepared by subjecting the compound (Ig) or a alt thereof The object compound (If) or a salt thereof can be to protecting reaction of carboxy.

റന്ന് Antional manner such as The ones described in Examples . This reaction can be carried out according to a or the similar manners thereto.

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Process 8

prepared by subjecting a compound (Ih) or a salt thereof The object compound (Ii) or a salt thereof can be to elimination reaction of amino protective group.

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to that of Process 4 mentioned in the above, and therefore the reaction mode and reaction conditions [e.g. reactive This reaction can be carried out in a similar manner etc.] of this derivative, solvent, reaction temperature

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reaction are to be referred to those as explained in Process 4

Process 9

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prepared by subjecting the compound (Ii) or its reactive The object compound (Ih) or a salt thereof can be derivative at the amino group, or a salt thereof to acylation reaction.

Suitable acylating agent to be used in the present acylation reaction may include the compound of the formula

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(wherein R^{10} is acyl as mentioned befere) or its reactive derivative, or a salt thereof.

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aldehyde, ketone or the like; a silyl derivative formed by N-trimethylsilylacetamide or the like; a derivative formed the compound (Ii) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction Suitable reactive derivative at the amino group of the reaction of the compound (Ii) with a silyl compound of the compound (Ii) with a carbonyl compound such as by the reaction of the compound ((Ii) with phosphorus such as N, O-bis(trimethylsilyl) acetamide, trichloride or phosgene; and the like.

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ester, and the like. The suitable example may be an acid Suitable reactive derivative of the compound (X) may chloride; acid azide; a mixed acid anhydride with an acid inglude and acid halide, an acid anhydride, an activated acid, sulfurous acid, thiosulfuric acid, alkanesulfonic nalogenated phosphoric acid, etc.), dialkylphosphorous acid (e.g., methanesulfonic acid, ethanesulfonic acid, diphenylphosphoric acid, dibenzylphosphoric acid, dialkylphosphoric acid, phenylphosphoric acid, such as substituted phosphoric acid (e.g.,

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acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, with imidazole, 4-substituted imidazole, dimethylpyrazole, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic etc.); a symmetrica acid anhydride; an activated amide carboxylic acid (e.g., pivalic acid, pentanoic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic triazole or tetrazole; an activated ester (e.g., syanomethyl ester, methoxymethyl ester,

propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl iimethyliminomethyl [(CH₃)₂*N=CH-] ester, vinyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester carboxymethyl thioester, pyranyl ester, pyridyl ester, ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenyl thioester, p-cresyl thioester, with a N-hydroxy compound. (e.g.,

N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, optionally be selected from them accordingly to the kind N, N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, etc.); and the like. These reactive derivatives can N-hydroxysuccinimide, N-hydroxybenzotriazole, of the compound' (Ii) to be used.

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The reaction is usually carried out in a conventional solvent such 'es 'water, acetone, dioxane, acetonitrile, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, adversely affect the reaction, or the mixture thereof. pyridine or any other organic solvents which do not chloroform, methylene chloride, ethylene chloride,

agent such as N,N*-dicyclohexylcarbodiimide; N-cgslohexylits salt form in the reaction, the reaction is preferably When the compound (Ii) is used in free acid form or carried out in the presence of a conventional condensing N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4diethylaminocyclohexyl)carbodiimide;

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N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-35

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methylimidazole); pentamethyleneketene-N-cyclohexylimine; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-lH-benzotriazole; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl so-called Vilsmeier reagent prepared by the reaction of sulfophenyl)isoxazolium hydroxide intra-molecular salt; N,N-dimethylformamide with thionyl chloride, phosgene, dimethylaminopropyl)carbodiimide; N, N-carbonyl-bis(2chloride); phosphorous trichloride; thionyl chloride; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(mpolyphosphate; phosphorous oxychloride (phosphoryl diphenylketene-N-cyclohexylimine; ethoxyacetylene; phosphorous oxychloride, etc.; or the like. oxalyl chloride; triphenylphosphite;

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The reaction may also be carried out in the presence N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, or the like.

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reaction is usually carried out under cooling to heating, The reaction temperature is not critical, and the

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The processes for preparing the starting compounds (IV) and (V) are explained in detail in the following. というなななないのではないないないのである。 九 日前に軍は後軍

Process A

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complianisting that it

derivative stathe earboxy group or a salt thereof with a compound (VIII) or its reactive derivative at the amino The object compound (IX) or a salt thereof can be prepared by reacting a compound (II) or its reactive group or a salt thereof.

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to that of Process 1 mentioned in the above, and therefore This reaction can be carried out in a similar manner the reaction mode and reaction conditions [e.g. reactive derivative, solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in

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Process 1.

· j.

prepared by subjecting a compound (IX) or a salt thereof to elimination reaction of the carboxy protective group. The object compound (IV) or a salt thereof can be

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to that of Process 4 mentioned in the above, and therefore This reaction can be carried out in a similar manner this reaction are to be referred to those as explained in acid, catalyst, solvent, reaction temperature, etc.) of the reaction mode and reaction conditions [e.g. base,

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the invention the case that amino protective group in \mathtt{R}^1 The present invention includes within the scope of is transformed into amino.

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Process C

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The object compound (Va) or a salt thereof can be prepared by reacting a compound (6) with acid.

Compound (6) can be prepared as follows.

(1) with formalin, and both compound (4) and compound (5) Compound (2) can be prepared by reacting a compound

(3) to Lipase-catalyzed reaction, and compound (6) can be prepared by reacting compound (5) with aqueous ammonia.

The reaction of each scep can be carried out in a conventional manner such as the ones described in Preparations

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ъ The object compound (Vb) or a salt thereof can prepared by reacting a compound (11) with acid. Compound (11) can be prepared as follows.

Compound (Fr can be prepared by reacting a compound

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(7) with a compound (8) (wittig reaction), and compound (11) can be prepared by reacting a compound (9) with a compound (10).

The reaction of each step can be carried out in a conventional manner such as the ones described in Preparations

mentioned processes is in a free form, it can be converted salt form, it can be converted into a free form or another hand, when the object compound (I) thus obtained is in a When the object compound (I) obtained by the aboveinto a salt form in a conventional manner. On the other salt form also in a conventional manner.

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The compounds obtained by the above Processes 1 to 9 and \underline{A} to \underline{D} can be isolated and purified by a conventional method such as pulverization, recrystallization, columnchromatography, reprecipitation of the like.

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carbon atom(s) and double bond(s) and all such isomers and (I) may include one or more stereoisomer such as optical It is to be noted that each of the object compound isomer(s) and geometrical isomer(s) due to asymmetric mixture thereof are included within the scope of this invention.

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representative compound (I) of the present invention are Now in order to show the utility of the object compound (I), some pharmacological test data of the shown in the following.

Test 1 : Effect on platelet aggregation induced by denosine diphosphate (ADP

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Test Compound

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(1) the compound of Example 21 (3)

E)

platelets/ml was prepared from human blood. To the 225 µl HEMA-TRACER 801). Activity of inhibitor (test compound) To the solution 5 µl of Platelet rich plasma (PRP) which contains 3×10^{8} ADP (final 2.5 μM) was added as an aggregation inducer. Aggregation was measured by using an aggregometer (NBS of PRP, 25 µl of drug solution* was added, and then was expressed as ${\rm IC}_{100}$ value i.e. dose required for complete inhibition of platelet aggregation. stirred for 2 minutes at 37°C.

Drug solution* --- Test compound was dissolved in

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Test Result

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1.0 × 10-6 IC100 (M) Test Compound (7)

carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), preparation, for example, in solid, semisolid or liquid oral or parenteral (including subcutaneous; intravenous pharmaceutically acceptable salt thereof, as an active invention can be used in the form of a pharmaceutical subjuggedient in admixture with an organic or inorganic and intramuscular) administrations or insufflation. The pharmaceutical composition of the present form, which contains the object compound (I) or a 25

The active ingrédient may be campounded, for example, insufflation, solutions, mulsions, suspensions, and any suppositories, creams, cintments, aerosols, powders for with the usual non-toxic, pharmaceutically acceptable other form suitable for use. And, if necessary, in carriers for tablets, pellets, troches, capsules,

addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be used.

produce the desired effect upon the process or condition pharmaceutical composition in an amount sufficient to The object compound (I) or a pharmaceutically acceptable salt thereof is/are included in the of the diseases.

generally used in this field of the art for improving the invention can be manufactured by the conventional method in this field of the art. If necessary; the technique pharmaceutical composition of the present invention. The pharmaceutical composition of the present bioavailability of a drug can be applied to the

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For applying the composition to a human being or an (including i.v. infusion), intramuscular, pulmonary, or oral administration, or insufflation including aerosols from metered dose inhalator, nebulizer or dry powder animal, it is preferable to apply it by intravenous inhalator.

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While the dosage of therapeutically effective amount of the object compound (I) varies from and also depends intramuscular administration, a daily dose of 0.001-100 mg or an animal, in case of oral administration, a daily dose prevention and/or the treatment of aforesaid diseases in a daily dose of 0.001-100 mg of the object compound (I) per of the object compound (I) per kg weight of a human being upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a a human being or an animal in generally given for the of 0.001-200 mg of the object compound (I) per kg weight kg weight of a human being or an animal, in the case of

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human being or an animal.

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The following <u>Preparations</u> and <u>Examples</u> are given for the purpose of illustrating the present invention in more

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Preparation 1

the mixture was poured into water and extracted with ethyl dimethylaminopropyl)carbodiimide (2.16 ml) under stirring 3-/ 1-text-butoxycarbonyl-4-piperidyl)propionic acid (3.04 at 0°C. After stirring at ambient temperature overnight, (1) To a mixture of (R)-etlyl nipecotinate (1.86 g), dimethwlformamide (20 ml) was added 1-ethyl-3-(3g) and 1-hydroxybenztriazole (1.60 g) in N,N-

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acetate. The extract was washed with water, brine and dried over MgSO₄, and evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with (CHCl3:MeOH) = (100:1) to give (R)-ethyl l-[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3-piperidinecarboxylate as an oil (4.01 g).

IR (Film): 2960, 2900, 2840, 1710, 1665, 1630 cm⁻¹

NMR (CDCl₃, 5): 1.00-1.20 (1H, m), 1.28 (3H, t, J=7.1Hz), 1.45 (9H, s), 1.48-1.88 (9H, m), 1.98-2.15 (1H, m), 2.31-2.51 (3H, m), 2.62-3.12 (4H, m), 3.35-3.47 (1/2H, m), 3.65-3.85 (1H, m), 4.00-4.22 (4H, m), 4.56-4.69 (1/2H, m)

Mass (m/z): 397 (M⁺+1)

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The following compounds were obtained according to a similar manner to that of Preparation 1 (1).

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(2) Ethyl 1-[2-(1-benzyloxycarbonyl-4-piperidyloxy)acetyl]-3-piperidinecarboxylate
IR (Film): 2930, 2860, 1720, 1690, 1640 cm⁻¹
NMR (CDCl₃, 6): 1.25 (3H, t, J=7.1Hz), 1.46-1.94
(7H, m), 2.00-2.16 (1H, m), 2.40-2.59 (1H, m), 2.85-3.40 (4H, m), 3.56-3.64 (1H, m), 3.73-3.98
(3H, m), 4.04-4.32 (2+1/2H, m), 4.15 (2H, q, J=7.7Hz), 4.49-4.60, (1/2H, m), 5.12, (2H, s), 7.30-7.37 (5H, m)
Mass (m/z): 433 (M⁺+1)

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(3) (R)-Ethyl: 1-[3-(1-benzyloxycarbonyl-4-piperidyl)propionyl]-3-piperidinecarboxylate.

IR (Film): 2980, 2920, 2840, 1715, 1690, 1630 cm⁻¹

NWR (CDCl₃, 6): 1.05-1.30 (5H, m), 1.40-1.88 (8H, m), 1.98-2.15 (1H, m), 2.30-2.50 (3H, m), 2.70-3.10 and 3.35-3.47 (total 4H, m), 3.67-3.83 (1H, m), 3.98-4.21 and 4.55-4.66 (total 5H, m), 5.12

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(2H, s), 7.29-7.37 (5H, m) Mass (m/z) : 431 (M⁺+1)

- (4) Methyl l-[3-(1-tert-butoxycarbonyl-4
 piperidyl)propionyl]-3-pyrrolidinecarboxylate

 IR (Film): 3450, 1730, 1680, 1630 cm⁻¹

 NMR (CDCl₃, 6): 1.07-1.18 (2H, m), 1.453 (9H, s),

 1.57-1.69 (3H, m), 1.63 (3H, s), 2.12-2.31 (3H,

 m), 2.61-2.73 (2H, m), 3.02-3.20 (1H, m), 3.45
 3.75 (7H, m), 4.05-4.15 (2H, m)

 Mass (m/z): 369 (M⁺+1)
- (5) 3-(3-(1-tert-butoxycarbonyl-4piperidyl)propionyl]aminopyridine
 mp: 152-153°C

 IR (Nujol): 1680, 1600 cm⁻¹

 NWR (CDCl3, 6): 1.00-1.20 (2H, m), 1.45 (9H, s),
 1.40-1.51 (1H, m), 1.61-1.75 (4H, m), 2.43 (2H,
 t, J=7.6Hz), 2.39-2.46 (2H, m), 4.03-4.14 (2H,
 m), 7.28 (1H, t, J=7.0Hz), 8.22 (1H, dd, J=5.7

 and 2.3Hz), 8.32 (1H, dd, J=4.7 and 1.4Hz), 8.59
 (1H, d, J=2.4Hz), 8.65 (1H, s)

 Mass (m/z): 334 (M⁺+1)

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- (6) Ethyl (S)-I [3-(1+tert-butovy-carbonyl-4-piperidyl)propionyl] 3-piperidinecarboxylate

 IR (Film): 2930, 2860, 1720, 1680, 1635 cm⁻¹

 WMP (Cicl3): 6): 1.03-1.23 (2H, m); 1.27 (3H, t, I=7.1Hz), 1.45 (9H, s), 1.53-1.74 (9H, m), 1.98-2.15 (1H, m), 2.32-2.51 (5H, m), 2.60-3.11 (4H, m), 3.68-3.86 (1H, m), 4.03-4.22 (4H, m)

 Mass (m/z): 397 (M+1)
- (7) N:[(R)-(1-benzyloxycarbonyl)-3-piperidylcatbonyl]-2(S)-text-butoxycarbonylamino-β-alanine ethyl ester

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IR (Film): 3320, 2975, 2930, 2860, 1700, 1680, 1660 cm⁻¹

NMR (CDCl₃, 6): 1.23-1.32 (1H, m), 1.28 (3H, t, J=7:1Hz), 1.43 (9H, s), 1.47-1.67 (4H, m), 1.72-2.03 (2H, m), 2.23-2.40 (1H, m), 3.45-3.90 (4H, m), 4.13-4.25 (3H, m), 4.31-4.42 (1H, m), 5.16 (2H, d, J=6.7Hz), 7.36-7.39 (5H, m)

(8) N-(3-Pyridyl)-3(S)-(tert-butoxycarbonylamino)succinamic acid methyl ester

IR (Film): 2975, 1700, 1680, 1600 cm⁻¹

NMR (CDCl₃, 6): 1.49 (9H, s), 2.77 (1H, dd, J=17.1

and 6.2Hz), 3.05 (1H, dd, J=17.1 and 4.4Hz),
3.74 (3H, s), 4.63-4.72 (1H, m), 5.91-6.00 (1H,
m), 7.23-7.30 (1H, m), 8.11 (1H, dq, J=8.3 and
1.0Hz), 8.36 (1H, dd, J=4.8 and 1.4Hz), 8.59

(1H, d, J=2.4Hz), 8.83-8.87 (1H, br)

Mass (m/z): 324 (M⁺+1)

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(9) N-[(3-Pyridyl)-2(S)-(tert-butoxycarbonylamino)]succinamic acid ethyl ester .r r

mp. 134-135°C

Money Republication in 3300, 1720, 1680, 1565 cm-1

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NWR (CDCl3, 6): 1.28 (3H, t. J=7,1Hz), 1.45 (9H, s), 2.96 (1H, dd, J=16.1 and 4.6Hz), 3.09 (1H, dd, J=16.1 and 5.2Hz), 4.24 (2H, q; J=7.1Hz), 4.58 (1H, dt, J=8.3 and 4.9Hz), 5.71-5.75 (1H, m), 7.24-7.30 (1H, m), 8.13-8.20 (1H, m), 8.32-8.37 (1H, m), 8.43-8.47 (1H, m), 8.57-8.61 (1H,

Mass (m/z): 338 (M^++1)

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(10) N-[(3-Pyridyl)-3(R)-(tert-butoxycarbonylamino)]succinamic acid benzyl ester

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IR (Film): 2970, 1705, 1670 cm-1

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NMR (CDCl₃, 6): 1.47 (9H, s), 2.83 (1H, dd, J=15.6 and 6.3Hz), 3.07 (1H, dd, J=17.1 and 4.7Hz), 4.65-4.75 (1H, m), 5.15 (2H, s), 5.93 (1H, d, J=8.4Hz), 7.21-7.27 (1H, m), 7.33 (5H, s), 8.07 (1H, dq, J=8.3 and 1.0Hz), 8.35 (1H, dd, J=4.7 and 1.4Hz), 8.57 (1H, d, J=2.4Hz), 8.87 (1H, s) Mass (m/z): 4.00 (M⁺+1)

Preparation 2

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(1) A solution of (R)-ethyl 1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3-piperidinecarboxylate (3.99 g) in a mixture of methanol (10 ml), tetrahydrofuran (10 ml) and water (10 ml) was added lithium hydroxide (1.27 g) under stirring at 0°C. After stirring at ambient temperature for 1 hour, the mixture was acidified with 5% KHSO4 aqueous solution and extracted with ethyl acetate. The extract was washed with water, brine and dried over MgSO4, and evaporated in vacuo to give (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3-piperidinecarboxylic acid (3.34 g).

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mp: 102-104°C IR (Nujol): 1720, 1680, 1630 cm-1 NMR (DMSO-d6, F): 0.84-1.10 (2H, m), 1.38-1.76 (8H, m), 1.38 9H, S), 1.82°.2.01 (1H, m), 2.20-2 4F

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MARK (DMSO-d6, "); 0.84-1.10 (2H, m), 1.38-1.76 (8H m), 1.38 9H, s), 1.82.201 (1H, m), 2.20-2.45 (3H, m), 2.59-2.76 (2H, m), 2.89-3.09 (1H, m), 3.28-3.40 (1H, m), 3.69-3.98 and 4.31-4.44 (total 4H, m)-

The following compounds were obtained according to a similar manner to that of <u>Preparation 2 (1)</u>.

(2) (R)-1-[3-(1-Benzyloxycarbonyl-4-piperidyl)propionyl]3-piperidinecarboxylic acid
mp : 134-135°C

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IR (Nujol): 1715, 1680, 1600 cm-1

m), 3.69-3.84 and 4.34-4.42 (total 2H, m), 3.95-NMR (DMSO-d₆, 6) : 0.90-1.10 (2H, m), 1.30-1.73 (8H, m), 1.85-1.98; (1H, m), 2.20-2.49 (3H, m), 2.65-2.86 (2H, m), 2.94-3.06 (1H, m), 3.27-3.38 (1H, 4.02 (2H, m), 5.06 (2H, s), 7.27-7.41 (5H, m), 12.38 (1H, s)

Mass (m/z): 403 (M^++1)

1.28-1.74 (8H, m), 1.87-2.01 (1H, m), 2.15-2.79 NMR (DMSO-d₆, 6) : 0.88-1.09 (2H, m), 1.38 (9H, s), (6H, m), 2.94-3.08 (1H, m), 3.70-3.94 (4H, m), piperidyl)propionyl]-3-piperidinecarboxylic acid IR (Nujol) : 3100, 1720, 1680, 1620, 1600 $m cm^{-1}$ (3) (S)-1-[3-(1-tert-butoxycarbonyl-4-Mass (m/z): 269 (M+1-Boc) 12.31-12.49 (1H, br) mp : 111-112°C 10 15

Preparation 3

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piperidyloxy)acetyl]-3-piperidinecarboxylate (2.06 g) and with water, brine and dried over $MgSD_{q\gamma}$ and evaporated in vacuo. The residue was recrystallized from diethyl ether to give 1-[2-(1-benzyloxycarbonyl-4-piperidyloxy)acetyl]and extracted with ethyl acetate. The extract was washed $\sim 10^{100} {\rm MeV}$ mixture was acidified with 10% aqueous solution of KHSO4 25 Was stirted for 1 hour at ambient temperature. The (1) A mixture of ethyl 1-[2-(1-benzyloxycarbonyl-4-J.N NaOH aqueous solution (14.29 ml) in a solution of 3-piperidinecarboxylic_acid (1.51 g).

mp : 102-104°C

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NMR (DMSO-d₆, 6): 1.34-2.00 (8H, m), 2.23-2.50 (1H, m), 2.73-3.86 (9H, m), 4.14-4.36 (2H, m), 5.07 IR (Nujol) : 1720, 1690, 1615, 1600 cm⁻¹

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(2H, s), 7.28-7.42 (5H, m), 12.34-12.55 (1H, br) Mass (m/z) : 405 (M+1)

The following compound was obtained according to similar manner to that of Preparation 3 (1) (2) 1-{3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3pyrrolidinecarboxylic acid

mp : 102-103°C

IR (Nujol) : 1720, 1680, 1480 cm⁻¹

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1.60-1.66 (2H, m), 1.94-2.08 (2H, m), 2.11-2.23 NMR (DMSO- d_6 , 6): 0.92-0.98 (2H, m), 1.38 (9H, s), (2H, m), 2.52-2.66 (2H, m), 2.96-3.14 (1H, m), 3.33-3.68 (7H, m), 3.88-3.94 (2H, m)

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Preparation 4

azidomethyl-2(S)-(tert-butoxycarbonyl)aminopropionate (1.5 serine ethyl ester (5 g) in N,N-dimethylformamide (50 ml) was added sodium azide (2.09 g) under stirring at ambient (1) To a solution of N-tert-butoxycarbonyl-o-mesyl-(L)dried over MgSO $_4$, and evaporated in vacuo. The residue The extract was washed with water, brine and mixture was poured into water and extracted with ethyl temperature. After stirring at 60°C for 3 hours, the eluting with (n-hemane:EtOAc = 7:1) to give ethyl 3was purified by column chromatography on silicatel

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J=7.1Hz), 4.41-4.51 (1H, m), 5.34-5.45 (1H, m) : NWR (CDC13, 5) : .1.31 (3H, t, J=7.1Hz), 1.46 (9H, s), 3.73 (1H, d, J=3.6Hz), 4.26 (2H, IR (Film): 3450, 2960, 2090, 1700 cm⁻¹ Mass (m/z) :.. 159 (M+1-Boc) .

The following compound was obtained according to a similar manner to that or Preparation 4 (1)

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(2) N-(Benzyloxycarbonyl)-3(S)-azidomethyl-\$-alanine tert-butyl ester
IR (Film): 3300, 2100, 1720 cm⁻¹
NMR (CDCl₃, 6): 1.44 (9H, s), 2.51 (2H, d, J=6.0Hz), 3.48-3.52 (2H, m), 4.08-4.18 (1H, m), 5.11 (2H, s), 5.40 (1H, br), 7.34-7.36 (5H, m)
Mass (m/z): 333 (M⁺-1)

Preparation 5

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A mixture of ethyl 3-azido-2(S)-(tert-butoxycarbonyl)aminopropionate (0.5 g) and 10% Pd-C (0.1 g, 50% wet) in ethanol (5 ml) was hydrogenated at atmospheric pressure for 1 hour. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo to give 2(S)-(tert-butoxycarbonyl)amino-β-alanine ethyl ester (0.45 g).

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IR (Film): 3350, 2960, 1720, 1680, 1650 cm⁻¹

NMR (DMSO-d₆, δ): 1.17 (3H, t, J=7.4Hz), 1.39 (9H, s), 1.30-1.85 (3H, m), 2.75-2.78 (1H, m), 3.33-3.49 (1H, m), 4.07 (2H, q, J=7.1Hz), 6.80-6.89 and 7.11-7.23 (total 1H, m)

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rhe following compound was obtained according to a similar manner tothab obtained to 5 (1). The similar manner tothab obtained to a similar manner to the similar manner to the

(2) 2(S)*Acetylamino-\$-alanine ethyl ester

(\$\alpha\$]_{5}^{2} = -35.9° (C=1.0, EtOH)

TR (Film): 1740, 1630 cm^1

NMR (DMSO-d₆, 6): 1.20 (3H, t, J=7.1Hz), 1.89 (3H, s), 2.99-3.23 (2H, m), 4.11 (2H, q, J=7.1Hz), 4.46-4.57 (1H, m), 8.30 (2H, br), 8.63 (1H, d,

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J=7.68Hz) Mass (m/z): 175 (M^++1)

35 Preparation 6

To a solution of N-text-butoxycarbonyl-L-serine ethyl ester (8.20 g) in tetrahydrofuran (300 ml) was added triphenylphosphine (10.15 g, 387 m mol), diethyldiazocarbonate (6.09 ml, 38.7 m mol) and diphenylphosphonic acid (8.34 ml, 38.7 m mol) successively at -5°C. After stirring at room temperature for 3 hours, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, saturated aqueous NaHCO3 solution and brine, dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with (EtOAc:n-hexane = 10:90) to give ethyl 3-azido-2(S)-(text-butoxycarbonylamino)propionate (5.0 g).

IR (Film): 3450, 2960, 2090, 1700 cm⁻¹

NMR (CDCl₃, 6): 1.31 (3H, t, J=7.1Hz), 1.46 (9H, s), 3.73 (1H, d, J=3.6Hz), 4.26 (2H, q, J=7.1Hz), 4.41-4.51 (1H, m), 5.34-5.45 (1H, m)

Mass (m/z): 159 (M⁺+1-Boc)

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20 Preparation 7

To a solution of ethyl 3-azido-2(S)-(text-butoxycarbonylamino)propionate (0.5 g) in ethyl acetate (5 ml) was added 4N HCl in ethyl acetate (5 ml) at 0°C.

After stirring at room temperature for 2 hours, the mixture was evaporated in vacuo. The residue was recrystallized from diethyl ether to give ethyl 2(S)-amino-3-azidopropionate hydrochloride (0.3 g).

NMR. (DMSO-46, 8): 1.25 (3H, t, J=7.1Hz), 3.97 (2H,

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MASS (m/z): 1.23 (2H, G, J=7.1Hz), 4.34 (1H, t, J=4.0Hz)

Mass (m/z): 159 (M⁺+1) free of compound

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Preparation 8

(1) To a solution of 3-aminopyridine (1 g) in 35 dichloromethane (10 ml) was added triethylamine (1.63 ml)

gel eluting with (CHCl $_3$:MeOH = 100:1), and recrystallized with water, saturated agueous NaHCO3 solution, water and stirring at 0°C. After stirring at ambient temperature and 3-methoxycarbonylpropionyl;chloride (1.44 ml) under extracted with dichloromethane. The extract was washed residue was purified by column chromatography on silica from diethyl ether to give N-(3-pyridyl)succinamic acid brine, and dried over MgSO4, and evaporated in vacuo. for 1 hour, the mixture was poured into water and methyl ester (0.73 g).

NMR (CDCl₃, 5): 2.66-2.81 (4H, m), 3.72 (3H, s), 7.22-7.29 (1H, m), 8.32 (1H, dd, J=8.3 and IR (Nujol) : 1730, 1685, 1610 cm⁻¹ 1.2Hz), 8.58 (2H, d, J=8.6Hz) Mass (m/z): 209 (M^++1) mp : 78-79°C

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The following compound was obtained according to similar manner to that of <u>Preparation 8 (1)</u>

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... NWR (CDC13, 6) .: 1.32 (3H, t, J=7.1Hz), 2.07 (3H, (21, 3,69-3,85 ((2H;mm),234-27 ((2H;247), J=7.1Hz)) (2) Ethyl 2(S)-acetylamino-3-azidopropionate IR (Film) : 3300, 2100, 1720, 1650 cm⁻¹ 4.70-4,773(1H;ngm),8:6;(36:(1H; br); Mass (m/z) 2013(M+1)

Frebaration 9

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After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was recrystallized and 10% Pd-C (0.86 g, 50% wet) in tetrahydrofuran (50 ml) butoxycarbonylamino)succinamic acid benzyl ester (4.28 g) was hydrogenated at atmospheric pressure for 2 hours. from diethyl ether to give N-(3-pyridyl)-3(R)-(tert-A mixture of N-(3-pyridy1)-3(R)-(tert-

butoxycarbonylamino)succinamic acid (2.55 g)

mp: 98-100°C

IR (Nujol) : 3430, 1735, 1700, 1680 cm⁻¹

3.33-3.46 (1H, m), 4.39-4.50 (1H, m), 7.27-7.38 NMR (DMSO-d₆, 6) : 1.39 (9H, s), 2.57-2.77 (2H, m), (2H, m), 8.03-8.07 (1H, m), 8.26-8.28 (1H, m), 8.76 (1H, s), 10.28 (1H, s)

Preparation 10

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with water and brine, and dried over MgS 0_4 , and evaporated temperature for 4 days, the mixture was poured into water and extracted with ethyl acetate. The extract was washed ml) was added to a solution of ethyl bromide (1.76 g) in nydrogen carbonate (0.54 g) in N,N-dimethylformamide (5. N,N-dimethylformamide (5 ml). After stirring at room chromatography on silica gel eluting with (CHCl $_3$:MeOH butoxycarbonylamino)succinamic acid (1 g) and sodium To a suspension of N-(3-pyridy1)-3(R)-(textin vacuo. The residue was purified by column 100:1) to give N-(3-pyridyl)-3(R)-(tert-

. 15

butoxycarbonylamino)succinamic acid ethyl ester (0.63 g) as an oil

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.. IR (Film) : 2980, 2940, 1715, 1675 cm⁻¹

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4.60-4.72 (lH, m), 5.86-5.96 (lH, m), 7.23-7.30 s), 2.76 (i.f., dd, J=17.2 and 6.4Hz), 3.04 (1H, (1H, m), ..8.10 (1H, dq, J=8.3 and 1.1Hz), 8.36 dd, J=17.2 and 4.3Hz), 4.19 (2H, q, J=7.1Hz), NMR (CDCl3, 6) : 3.28 (3H, t, J=7.1Hz), 1.49 (9H, (lH, dd, J=4.7 and 1.4Hz), 8.59 (lH, d,

J=2.4Hz), 8.76-8.81 (iH, br)

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Mass (m/z): 338 (M++1)

Preparation 11

butoxycarbonylamino)sucinamic acid methyl ester (3.91 (1) A mixture of N-(3-pyridy1)-3(S)-(tert-35

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and 4N HCl in dioxane (3.36 ml) and PtO₂ (0.39 g) in methanol (40 ml) was hydrogenated at atmospheric pressure for 2 hours. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was recrystallized from diethyl ether to give N-(3-piperidyl)-3(S)-(tert-butoxycarbonylamino)succinamic acid methyl ester hydrochloride (3.67 g).

IR (Nujol) : 1740, 1680, 1640 cm⁻¹

NMR (DMSO-d₆, δ) : 1.38 (9H, s), 1.64-1.95 (4H, m),
2.48-2.92 (3H, m), 3.08-3.20 (2H, m), 3.60 (3H,
d, J=5.1Hz), 3.83-4.04 (2H, m), 4.20-4.43 (1H,
m), 7.06-7.20 (1H, m), 8.12-8.29 (1H, m)

Mass (m/z) : 330 (M⁺+1) free of compound

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The following compounds were obtained according to a similar manner to that of <u>Preparation 11 (1)</u>.

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(2) N-(3-Piperidyl)succinamic acid methyl ester hydrochloride mp: 87-89°C IR (Nujol): 3300, 2920, 1720, 1640 cm⁻¹ NMR (DMSO-d₆, 6): 1.36-1.91 (5H, m), 2.34-2.40 (2H, m), m), 2.47-3.01 (3H, m), 3.04-3.20 (2H, m), 3.58 m), 2.47-3.01 (3H, m), 8.23 (1H, d), cj.(3H, s), 9.65-9.20 (1H, b), 8.23 (1H, d) Mass (m/z): 215 (M⁺+1) free of compound

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(3) N-(3-Piperidy1)-2(S)-(tert-butoxycarbonylamino)sucrinamic acid ethyl ester

IR (Film): \$406, 1840, 1700, 1640 cm⁻¹

NMR (DMSO-d₆, 6): 1.16 (3H, t, J=7.1Hz), 1.17-1.79

(6H, m), 1.37 (9H, s), 2.22-2.58 (2H, m), 2.712.93 (2H, m), 3.45-3.64 (1H, m), 4.06 (2H, H, H), J=7.1Hz), 4.29 (1H, q, J=7.4Hz), 7.04-7.10 (1H, m), 7.75 (1H, d, J=7.8Hz)

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Mass (m/z): 344 (M+1)

(4) 3-[[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]amino]piperidine
IR (Film): 3400, 2930, 1635 cm⁻¹

NMK (DMSO-d₆, 5): 0.85-1.04 (2H, m), 1.27-1.49 (5H, m), 1.38 (9H, s), 1.55-1.77 (5H, m), 1.99-2.40 (2H, m), 2.60-2.91 (5H, m), 3.46-3.64 (2H, m), 3.86-3.96 (2H, m), 7.63-7.67 (1H, m)

Mass (m/z): 340 $(M^{+}+1)$

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Preparation 12

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A mixture of N-(3-pyridy1)-3(R)-(tert-butoxycarbonylamino)succinamic acid ethyl ester (0.62 g) and PtO₂ (0.06 g) in acetic acid (12 ml) was hydrogenated at atmospheric pressure for 6 hours. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was dissolved in water. The solution was adjusted to pH 10 with saturated aqueous potassium carbonate solution, and extracted with ethyl acetate. The extract was washed with water and brine, and dried over MgSO₄, and evaporated in vacuo to give N-(3-piperidyl)-3(R)-(tert-butoxycarbonylamino)succinamic acid ethyl ester.(0.51 g) as an oil.

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IR (Film): 3500, 2980, 2940; 1710, 1660 cm⁻¹

NMR (DMSO-d₆, 5): 1.17 (3H, t, J=7.1Hz), 1.38 (9H, s), 1.32-1.70 (6H, l.), 2.28-2.88 (4H, m), 3.50-3.64 (1H, br), 4.20 (2H, q, J=7.1Hz), 4.20-4.33 (1H, m), 7.04-7.11 (1H, m), 7.59-7.63 (1H, m)

Mass (m/z): 344 (M⁺+1)

Preparation 13

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To a mixture of P (penzyloxycarbonyl)-3(S)-hydroxymathyl-β-alanine tert-butyl ester (3.1 g) and triethylamine (1.35 ml) in dichloromethane (25 ml) was

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dichloromethane (5 ml), under ice cooling. After stirring extract was washed with water, brine and dried over MgSO $_4$, give N-(benzyloxycarbonyl)-3(S)-methanesulfonyloxymethyl)added a solution of methanesulfonyl chloride (1.35 ml) in column chromatography on silica gel eluting with \mathtt{CHCl}_3 ·to The mixture was poured β -alanine tert-butyl ester (3.1 g) as an colorless oil. The residue was purified by into water and extracted with dichloromethane. IR (Film) : 3330, 1710 cm-1 at room temperature for 1 hour. and evaporated in vacuo.

5.11 (2H, s), 5.44-5.48 (1H, m), 7.35-7.42 (5H, m) 2.74 (1H, br), 2.98 (3H, s), 4.25-4:34 (3H, m), NMR (CDCl₃, 6): 1.44 (9H, s), 2.56-2.59 (2H, m),

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Preparation 14

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 $108 imes ext{c}$ and extract with ethyleacetate. The extract was washed with water, brine and dried over ω -tert-butyl ester (3.0 g) and triethylamine (1.55 ml) in stirring for 1 hour, the precipitate was filtered off and the filtrate was added to a solution of $NaBH_{d}$ (1.05 g) in stirring for 30 minutes, the mixture was neutralized with 49SO4, and evaporated in vacuo. The residue, was purified To a mixture of N-benzyloxycarbonyl(L)aspartic acid tetrahydrofuran (30 ml) was added ethyl chlorocarbonate .48. hydroxymethyl- β -alanine tert-butyl ester (2.5 g) as an by column chromatography on silica geletiting with 2% tetrahydrofuran (30 ml) - water (6 ml) at 0°C. After [1.06 ml] at -30°C under nitrogen atmosphere. After (MeOH/CHCl₃) to give N-(benzyloxycarbonyl)-3(S)colorloss oil. 20 25

3.68-3.73 (2H; m), 3.99-4.08 (1H, m), 5.10 (2H, NMR (CDC13, 6) : 71.43 (9H, 8); 2.53-2.57 (3H, S), m), 5.29-5.52 (1H, m), 7.35-7.37 (5H, m) IR (Film) : 3320, 1700 cm-1 Mass (m/z): 310 $(M^{+}+1)$

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Preparation 15

 A mixture of N-benzyloxycarbonyl-3(S)-hydroxymethyl-1.87 g), imidazole (0.66 g) and I_2 (1.80 g) was stirred The precipitate was N-benzyloxycarbonyl-3(S)-iodomethyl-\$-alanine tert-butyl 3-alanine tert-butyl ester (2.0 g), triphenylphosphine filtered off and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with 5% (EtOAc/n-hexane) to give for 30 minutes at room temperature. IR (Nujol): 3350, 1700 cm⁻¹ ester (1.8 g) as a white solid.

3.41-3.43 (2H, m), 3.91-3.98 (1H, m), 5.11 (2H, NMR (CDCl₃, 6): 1.44 (9H, s), 2.48-2.64 (2H, m), s), 5.30-5.35 (1H, m), 7.35-3.37 (5H, m)

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ø The following compound was obtained according to similar manner to that of Preparation 15 (1)

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3.32.95+9.03%(2H, m), 3.26-3.32 (2H, m), 4.00-4.10 s), 1.66-1.83 (4H, m), 2.54 (2H, d, J=6.0Hz), NMR (CDC13, 6): 0.93 (3H, t, J=7.2Hz), 1.43 (9H, (2) N-(Benzyloxycarbonyl)-3(S)-(n-butanesulfonyl)aminomethyl)- β -alanine tert-butyl ester 5.61 (1H, m), 7.35-7.37 (5H, m) IR (CHCl₃): 1710 cm⁻¹

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Mass (m/z): 429 (M^++1)

52

Preparation 15

additional 1 hour. The mixture was poured into water and dimethylformamide (6 ml) was added NaH (58 mg) under ice minutes, N-(benzyloxycarbonyl)-3(S)-iodomethyl- β -alanine cooling. After stirring at room temperature for 30 To a solution of thirphenol (0.15 ml) in N,Ntert-butyl ester (0.6 g) was added and stirred for

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extracted with ethyl acetate. The extract was washed with vacuo. The residue was purified by column chromatography (benzyloxycarbonyl 3-3(S)-phenylthiomethyl-\$-alanine terton silica gel eluting with 5% (EtOAc/n-hexane) to give Nwater, brine and dried over ${\rm MgSO}_4$, and evaporated in butyl ester (0.64 g) as an pale yellow oil.

IR (Film): 3320, 1720 cm-1

3.02-3.25 (2H, m), 4.10-4.38 (1H, m), 5.08 (2H, NMR (CDCl3, 6): 1.41 (9H, s), 2.50-2.66 (2H, m), s), 5.45-5.50 (1H, m), 7.18-7.38 (10H, m) Mass (m/z): 402 (M^++1)

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chloroform (10 ml) was added m-chloroperbenzoic acid (0.64 phenylthiomethyl-\$-alanine tert-butyl ester (0.60 g) in give N-(benzyloxycarbonyl)-3(S)-phenylsulfonylmethyl-\betaextract was washed with agueous ${\tt NaHSO}_3$ solution, water, brine and dried over ${\rm MgSO}_4$, and evaporated in vacuo to g) at 0°C. After stirring at room temperature for 2 hours, the mixture was poured into saturated aqueous alarine tert-butyl ester (0.4 g) as a colorless oil. NaHCO3 solution and extracted with chloroform. The To a solution of N-(benzyloxycarbonyl)-3(S)-IR (Film): 3350, 1720, 1520 cm-1

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3.36-3.46 (1H, m), 3.58-4.61 (lH, m), 4.33-4.37 (1H, m), 5.02 (2H, s), 5.37-5.65 (1H, m), 7.33-.«» 7;36 -(5H; 'm); -7.49-7.64 (3H, m), 7.88-7:92 (2H, NMR (CDCI3, 6): 1.42 (9H, s), 2:64-2.79 (2H, m),

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Preparation 18

Mass (m/z) : 434 (M+1)

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phenylsulfonylmethyl-ß-alanine tert-butyl ester (0.44 g) and 10% Pd-C (0.1 g, 50% wet) in acetic acid (5.ml) was (1) A mixture of N-(benzyloxycarbonyl)-3(S)-

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acetate and washed with saturated aqueous NaHCO $_{
m 3}$ solution. The catalyst was filtered off and the filtrate was hydrogenated at 1 atmospheric pressure of hydrogen for 1 The residue was dissolved in ethyl The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give 3(S)-phenylsulfonylmethyl-\$-alanine tertbutyl ester (0.3 g) as a colorless oil. evaporated in vacuo.

3.21-3.30 (2H, m), 3.68-3.78 (1H, m), 7.54-7.72 NMR (CDCl3, 6): 1.42 (9H, s), 2.31-2.52 (2H, m), IR (Film): 3570, 3370, 1710 cm-1 (3H, m), 7.91-7.96 (2H, m) Mass (m/z) : 300 (M+1)

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The following compound was obtained according to a similar manner to that of <u>Preparation 18 (1)</u>

13

NMR (DMSO-d6, 6) : 0.89 (3H, t, J=7.2Hz), 1.40 (9H, s), 1.54-2.13 (4H, m), 2.31-2.41 (1H, m), 2.81-(2) $3(S)-(n-butanesulfonylamino)methyl-\beta-alanine tert-$ 2.87 (2H, m), 2.94-3.02 (4H, m) Mass (m/z) : 295 (M+1) butyl ester

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reparation 19

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the resulting precipitates were collected by filtration to NMR (DMSO-d6, 6): 1.02-1.91 (7H, m), 2.21-2.35 (1H, added 4N UCl in ethyl acetate (2.1 ml) under stirring at 0°C. After stirring at ambient temperature for 2 hours, alanine ethyl ester (0.4 g) in ethyl acetate (4 ml) was $2(S_j$ -amino- β -alanine ethyl ester hydrochloride (0.31 g). give N-[(R)-1-benzyloxycarbonyl-3-piperidyl)carbonyl]- $\label{eq:piperidyl} $$ piperidyl) $$ carbonylamino $$ -\beta-$$$ To a solution of N-[(\mathbb{R})-(1-benz:loxycarbonyl-3-IR (Nujol) : 3300, 1/35, 1680, 1640 cm-1

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m), 2.80-2.89 (2H, m), 3.42-3.67 (2H, m), 3.90-

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4.15 (5H, m), 5.07 (2H, d, J=2.7Hz), 7.28-7.42 (5H, m), 8:43-8:49 (1H, m), 8:64-8:73 (2H, br) Mass (m/z): 378 (M^++j) free of compound

Preparation 20

brine, and dried over ${\rm MgSO_4}$, and evaporated in vacuo. The hydrochloride (300 mg) in dichloromethane (3 ml) was added rriethylamine (222 μ 1) and benzoyl chloride (93 μ 1) under with water, saturated aqueous NaHCO3 solution, water and residue was recrystallized from diethyl ether to give N^\perp stirring at 0°C. After stirring at ambient temperature extracted with dichloromethane. The extract was washed (R)-(1-benzyloxycarbonyl-3-piperidyl)carbonyl]-2(S)piperidy])carbonyl]-2(S)-amino- β -alanine ethyl ester A solution of N-[(R)-(1-benzyloxycarbonyl-3for 1 hour, the mixture was poured into water and benzoylamino- β -alanine ethyl ester (349 mg).

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d, 17=3.9Hz), 7.24-7.55 (10H, m), 7.85-7.95, (1H, m) 4.14-4.30 (2H, m), 4.78-4.89 (TH, m), 5.10 (2H, (6H, m), 2.26-2.43 (1H, m), 3.26-4.03 (5H, m), NMR (CDC13, 5) : 1.30 (3H, t, J=7.1Hz), 1.33-2.10 IR (Nujol) : 3290, 1730, 1685, 1655, 1640 cm $^{-1}$

... Mass (m/z) :- 482 (M+11)

Preparation 21

 ${\rm MgSO}_4$, and evaporated in vacuo. The residue (198 mg) was piperidy1)carbony1]-2(S)-amino- β -alanine hydrochloride in extracted with ethyl acetate. The extract was dried over dissolved in ethyl acetate (5 ml), and added NaHCO3 (269was removed by filtration, the filtrate was concentrated mg) and benzenesulfonyl chloride (136 µl). The mixture was refluxed for 4 hours. After the insoluble material water was made basic with aqueous K_2CO_3 solution, and (1) A solution of N-[(1R)-(1-benzyloxycarbonyl-3-

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piperidyl)carbonyl]-2(S)-phenylsulfonylamino-\b-alanine chromatography on silica gel eluting with (CHCl3:MeOH in vacuo. The residue was purified by column 100:1) to give N-[(R)-1-benzyloxycarbonyl-3ethyl ester as an bil (255 mg).

IR (Film): 1720, 1640 cm⁻¹

(7H, m), 2.23-2.50 (1H, m), 3.33-3.83 (3H, m), NMR (CDCl₃, 6): 1.12 (3H, t, J=7.1Hz), 1.40-2.11

(2H, q, J=10.0Hz), 7.31-7.40 (10H, m), 7.81-7.86 3.98 (2H, q, J=7.1Hz), 3.93-4.19 (1H, m), 5.16

(2H, m)

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Mass (m/z) : 518 $(M^{+}+1)$

The following compound was obtained according to similar manner to that of Preparation 21 (1)

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(2) N-[(R)-(1-benzyloxycarbonyl-3-piperidyl)carbonyl]- $2(S)-(n-butanesulfonylamino)-\beta-alanine ethyl ester$ IR (Film) : 2940, 2860, 1730, 1665 cm⁻¹

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NMR (CDCl₃, 6): 0.93 (3H, t, J=7.3Hz), 1.31 (3H, t, J=7.2Hz), 1.37-1.48 (4H, m), 1.56-1.84 (7H, m), 1.91-2.43 (IH, m), 2.97-3.05 (2H, m), 3.35-3.87 . . . 5.82-6.01 (1/2H, m), . . 6 «63=6.83 · (1/2H, m), 7.33-(4H, m), 4.15-4.31 (3H, m), 5.10-5:25:(2H, m),

Mass (m/z) : 498 (MT+1) 7.37 (5K; m)

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Preparation 22

To a solution of trimethylsilylacetylene (1715 ml) in chloride (2.0M solution in tetrahydrofuran; 6.19) was hour. After cooling to -30°C, 4-acetoxy-2-azetidinone added dropwise below $-30\,^{\circ}\mathrm{C}$ under nitrogen atmosphere. reaction mixture was allowed to 0°C and stirred for 1 (320 g) was added and warmed to room temperature, and tetrahydrofuran (18.0 %) was added ethyl magnesium

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was added and washed with water (10 ℓ x 2) and brine. The ammonium chloride (4.0 1) was added. Ethyl acetate (20 1) essentially pure, so it was used to the next step without organic layer was dried over magnesium sulfate, filtered stirred for 2 hours. After cooling to -20°C, saturated trimethylsilylethynyl)-2-azetidinone (425 g), which was off and evaporated in vacuo to give 4-(2further purification.

NMR (CDCl₃, 6): 0.16 (9H, s), 3.02 (1H, ddd, J=14.7 5.3 and 1.8Hz), 4.24 (1H, dd, J=5.3 and 2.7Hz), and 2.7 and 1.6Hz), 3.30 (1H, ddd, J=14.7 and IR (Nujol) : 3150, 2130, 1740, 1330, 1240, 1090, 1060, 950, 840, 750, 740 cm⁻¹ 6.41 (IH, br)

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Preparation 23

12

4-(2-Trimethylsilylethynyl)-2-azetidinone (485 g) and silica gel (CH₂Cl₂:EtOAc = 8:2) to give N-hydroxymethyl-4-IR (Nujol), 33300, 1710, 1280, 1230, 1020, 820 cm-1 STORESTON STATE (COCCESSIONS) : 0.48 (9H, S), 3.02 (1H, dd, J=14.8 ACE 25 Communication and 2.7Hz), 3.26 (1H, dd, J=14.8 and 5.4Hg), of temperature and purified with column chromatography on paraformaldehyde (261 g) was heated at 135°C for 45 minutes. The resulting mixture was cooled to room (2-trimethylsilylethynyl)-2-azetidinone (429 g). 20

3.69 (1H, dd, J=9.4 and 5.3Hz), 4.41 (2H, m),

5.01 (1H, dd, J=11.8 and 5.2Hz)

FAB-Mass : 197 (M⁺+1)

100 OF

Preparation 24 30

and Lipase PS (trademark; Amano Pharmaceutical Co., Ltd.) (190 g). The mixture was warmed to 37°C and stirred for dichloromethane (6.5 %) was added vinyl acetate (350 ml) trimethylsilylethynyl)-2-azetidinone (250 g) in To a solution of N-hydroxymethyl-4-(2-

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residue was subjected to silica gel column chromatography eluting with (n-hexane:EtOAc = 8:2 to 0:1) to give (R)-Ndichloromethane. Solvent was evaporated in vacuo. The hydroxymethyl-4-(2-trimethylsilylethynyl)-2-azetidinone 32 hours. Catalyst was filtered off and washed with (192 g).

NMR (CDCl3, 8): 0.18 (9H, s), 3.02 (1H, dd, J=14.8 IR (Nujol) : 3300, 1710, 1280, 1230, 1020, 820 cm-1 3.69 (1H, dd, J=9.4 and 5.3Hz), 4.41 (2H, m), and 2.7Hz), 3.26 (1H, dd, J=14.8 and 5.4Hz), 5.01 (1H, dd, J=11.8 and 5.2Hz) $[\alpha]_{50}^{0} = -133.9^{\circ} (C=1.12, CHCl_3)$ FAB-Mass : 197.8 (M⁺)

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Preparation 25

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was added (S)-N-hydroxymethyl-4-(2-trimethylsilylethynyl)at room temperature for overnight. Solvent was evaporated layer was dried over MgSO $_4$, filtered off and evaporated in The organic 2-azetidinone (101 g). The resulting mixture was stirred vacuo. The residue was purified by column chromatography on silica gel eluting with $(CH_2Cl_2:BtOAc = 9:1)$ to (S)-4in vacuo and the residue was added ethyl acetate (1.5 ℓ) To aqueous ammonia (300 ml) and methanol (1000 ml) and washed with water (100 ml \times 3) and brine. ethynyl-7-szetidinone (29.8 g).

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NMR (CDCl3, 6): 2.46 (1H, d, J=2.0Hz), 3.11 (1H, IR (Nujol): 3200, 2080, 1400, 1320, 1160 cm⁻¹ $[\alpha]\hat{b}^0 = -63.3^{\circ} (C=1.09, CHCl_3)$

ddd, J=14.8 and 2.5 and 1.6Hz), 3.35 (1H, ddd, J=14.8 and 5.3 and 1.8Hz), 4.27 (1H, m), 6.46 (1H, br)

Preparation 26

To a solution of (S).4-ethynyl-2-azetidinone (28.5 g) in ethanol (140 ml) was added a solution of HCl in ethanol

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enantiomers was determined to be 98.5:1.5 by chiral HPLC The residue was washed with diethyl ether and collected by lydrochloride (50.3 g) as white crystal. The ratio of emperature. The mixture was evaporated in vacuo. 5.86N) below 10°C, and stirred for 1 hour at room filtration to give ethyl (S)-3-amino-4-pentynoate using CROWNPAK CR(+) (trademark; DAICEL CHEMICAL INDUSTRIES, LTD.).

dd, J=16.1 and 9.1Hz), 3.07 (1H, dd, J=16.1 and NMR (DMSO-d₆, 6): 1.21 (3H, t, J=7.1Hz), 2.84 (1H, 5.0Hz), 4.13 (2H, q, J=7.1Hz), 4.29 (1H, m), IR (Nujol) : 3210, 2190, 1710, 1560 cm^{-1} $[\alpha]_{0}^{2} = -6.27^{\circ} (C=1.11, MeOH)$ Mass (m/z): 142 (M^++1) 8.94 (3H, br)

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Preparation 27

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To a solution of CBrd (3.11 g) in dichloromethane (15 sadichloromethane. The extract was washed with water, dried ml) was added dropwise a solution of triphenylphosphine butyldimethylsilyl-4-(2,2-dibromoethenyl)-2-azetidinone dichloromethane (10 ml) was added dropwise at 0°C and purified by chromatography on silica gel eluting with butyldimethylsilyl-4-formyl-2-azetidinone (1.0 g) in saturated agueous NaHCO3 solution and extracted (with.over MgSO4 and evaporated in vacuo. The residue was stirred for 20 minutes; The mixture was poured into (4.92 g) in dichloromethane (15 ml) at 0°C. After diethyl ether:n-hexane = 1:5) to give (S)-N-tertstirring for 10 minutes a solution of (S)-N-tert-(0.83 g) as a pale yellow oil.

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9H, s), 2:75 (1H, dd, J=2.8 and 15.6Hz), 3.30 NMR (CDCl₃, 6): 0.12 (3H, s), 0.16 (3H, s), 0.85 (lH, dd, J=5.6 and 15.6Hz), 4.13-4.22 (lH, m) IR (Film) : 3450, 3300, 1740, 1600 cm $^{-1}$

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6.38 (1H, d, J=8.8Hz) Mass (m/z): 370 (M++1)

Preparation 28

extracted with ethyl acetate. The extract was washed with jive (S)-N-tert-butyldimethylsilyl-4-ethynyl-2-azetidinone lithium bis(trimethylsilyl)amide (3.75 ml, 1 mol solution NMR (CDCl3, 6): 0.19 (6H, s), 0.88 (9H, s), 2.35 silica gel eluting with (diethyl ether:n-hexane = 1:5) hour, a saturated aqueous $\mathrm{NH_4Cl}$ solution was added and To a solution of (S)-N-tert-butyldimethylsilyl-4-2,2-dibromoethenyl)-2-azetidinone (0.63 g) was added n n-hexane) at -75°C. After stirring at -75°C for 1 racuo. The residue was purified by chromatography on *ater and brine, dried over $MgSO_4$, and evaporated in IR (Film) : 3420, 3250, 2100, 1720 cm⁻¹ $[\alpha]^{0}_{60} = -61.5^{\circ}$ (C=1.0, MeOH) (0.20 g) as an colorless oil. 10

15.1Hz), 3.28 (1H, dd, J=5.6 and 15.1Hz), 4.00-(1H, d, J=2.2Hz), 3.02 (1H, dd, J=3.0 and 4.05 (1H, m)

Mass (m/z): 210 (M^++1)

Preparation 29

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cchynyl-2-azetidinone (120 mg) was added 4N HCl in ethanol amino-4-pentynoate hydrochloride (50 ml) as a white solid The ratio of enantiomers was determined to be 99.5:0.5 by (2 ml) at room temperature. After stirring for 1 hour, To a solution of (S)-W-talt-butyldimethylsilyl-4recrystallized from diethyl ether to give ethyl (S)-3asthe mixture was evaporated in vacuo. The residue was chiral HPEC using CROWNPAK CR(+). $[\alpha]_{0}^{2} = -7.1^{\circ} (C=1.0, MeOH)$

NMR (DMSO-d6, 5): 1.21 (3H, t, J=7.1Hz), 2.84 (1H, IR (Nujol): 3210, 2190, 1710, 1550 cm-1

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dd, J=16.1 and 9.1Hz), 3.07 (1H, dd, J=16.1 and 5.0Hz), 4.13 (2H, q, J=7.1Hz), 4.29 (1H, m), 8.94 (3H, br)

Mass (m/z): 142 (M^++1)

Preparation 30

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To a mixture of zinc (11.9 g) in tetrahydrofuran (215 ambient temperature and the resultant mixture was stirred (S)-N-tert-butyldimethylsilyl-4-formyl-2-azetidinone (4.3 washed with water, saturated aqueous NaHCO $_{
m 3}$ solution and eluting with (EtOAc:n-hexane = 1:10) to give (S)-N-tertfor 1 hour. A solution of methyleneiodide (8.1 ml) was g) in tetrahydrofuran (130 ml) and stirred for 2 hours. the resultant mixture was added dropwise a solution of The mixture was poured into a mixture of diethyl ether butyldimethylsilyl-4-vinyl-2-azetidinone (2.13 g) as a then added to the mixture was stirred for 30 minutes. ml) was added titanium (IV) isopropoxide (6.0 ml) at (500 ml) and lN HCl (300 ml). The organic layer was residue was purified by chromatograph on silica gel brine, dried over ${\tt MgSO_4}$, and evaporated in vacuo. colorless oid.

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 $(\alpha)^{1/2} = -15.6^{\circ} (C=1.0, MeOH)$

IR (Film): 2940, 2860, 1730 cm 296 nurs (CDCI3/6) Pr (3H, s), 0.96 (9H, s), 2.77 (1H, dd, J=2.8 and 14.7Hz), 3.30

Ć! EJ Mass $(i\hbar/z)$: 21.2 (M^+1)

(1H, dd, J=5.6 and 14.7Hz), 3.97-4.06 (1H, m),

Preparation 31

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To a solution of (S)-N-text-butyldimethylsilyl-4-vinyl-2-azatidinone (1.0 g) in ethanol (5 ml) was added 6N HCl in ethanol (5 ml) at 0°C. After stirring for 1 hour, the mixture was evaporated in vacuo and the resultant

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solid was washed with diethyl ether to give ethyl (S)-3-amino-4-pentenoate hydrochloride (0.67 g) as a white solid.

 $[\alpha]_{50}^{0} = -8.9^{\circ} (C=1.0, MeOH)$

IR (Nujol) : "3420, 2100, 1720, 1600 cm⁻¹

NMK (DMSO-d₆, 6): 1.19 (3H, t, J=7.1Hz), 2.70 (1H, dd, J=8.4 and 16.0Hz), 2.91 (1H, dd, J=5.7 and 16.0Hz), 3.93-4.00 (1H, m), 4.05 (2H, q,

J=7.1Hz), 5.31 (1H, d, J=8.0Hz), 5.38 (1H, d, J=15.0Hz), 5.80-5.97 (1H, m), 8.54 (3H, br)

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Elemental Analysis C₇H₁₃NO₂·HCl·0.2C₂H₅OH Calcd.: C 47.11, H 8.01, N 7.42 Found : C 47.26, H 8.37, N 7.79

Example 1

15

(1) To a mixture of ethyl 3-amino-2-ethynylpropionate hydrochloride (0.5 g), (R)-1-[3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl]-3-piperidinecarboxylic acid (1.04 g) and 1-hydroxybenztriazole (0.38 g) in N,N-dimethylformamide (5 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.51 ml) under stirring

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dimethylationmamide (5 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodismide (0.51 ml) under stirring at 0°C. After stirring at ambient temperature overnight, the mixture was poured into water and extracture overnight, acetate. The extract was washed with we to brine and dried over MgSO₄, and evaported in vac.3. The residue was purified by chromatography on silica gel eluting with CHCl3:MeOH ** (100:1) to give N-[(R)-1-{3-(1-text-butoxycarbonyl-4-piperidyl)propionyl}-3-

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piperidylcarbonyl]-3-ethynyl-\$-alanine ethyl ester as an
oil (1.38 g).
IR (Film) : 3440, 3270, 2960, 2920, 2850, 1720,

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1710, 1640 cm⁻¹
NMR (CDCl₃ 5): 0.98-1.20 (1H, m), 1.28 (3H, t, J=7.1Hz), 1.45 (9H, s), 1.45-1.78 (8H, m), 1.85

J=7.1Hz), 1.45 (9H, s), 1.45-1.78 (8H, m), 1.89-2.07 (2H, m), 2.26-2.39 (4H, m), 2.61-2.74 (4H,

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m), 3.20-3.34 (2H, m), 3.53-3.69 and 3.82-3.97 (total lH, m), 4.02-4.50 (5H, m), 5.03-5.18 (lH, m), 6.80-6.90 and 7.06-7.16 (total lH, m)

Mass (m/z): 492 (M⁺+1)

The following compounds were obtained according to a similar manner to that of Example 1 (1).

07

(2) (3R)-N-[(R)-1-{3-(1-text-butoxycarbony1-4-piperidy1)propiony1}-3-piperidy1carbony1]-3-methy1-β-alanine methy1 ester

IR (Film): 3350, 2980, 2930, 2860, 1710, 1620 cm⁻¹

NMR (CDCl₃, 6): 1.02-1.15 (2H, m), 1.22 (3H, d, J=6.8Hz), 1.45 (9H, s), 1.34-1.79 (9H, m), 1.99-2.16 (1H, m), 2.05-2.73 (7H, m), 3.18-3.58 (2H, m), 3.67-3.70 (3H, m), 3.85-4.14 (3H, m), 4.29-4.49 (1H, m), 6.32-6.43 and 6.69-6.79 (total 1H, m))

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(3) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-piperidyl)-propionyl}-3-piperidylcarbonyl]-β-alanine ethyl ester
 IR (Film): 3420, 3300, 2920, 2850, 1725, 1665,

Mass (m/z): 468 $(M^{+}+1)$

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.NMR.(CDC13, 6) : I.600%L221 (2H; M), 1.27 (3H, t, J=7.1Hz), 1.45 (9H, S), 1.52-1.77 (7H, m), 1.83-2.09 (2H, m); 2:17-2.39 (3H, m); 2.48-2.73 (4H, m), 3.16-3.68 and 3.83-3:96 (total'5H, m), 4.02-4.25 and 4.36-4.99 (total 3H, m), 4.16 (2H, q, J=7.2Hz), 6.23-6.26 and 6.55-6.66 (total 1H, m) Mass (m/z): 468 (M+1)

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(4) N-[1-{2-(1-benzyloxycarbonyl-4-piperidyloxy)acetyl}-3-piperidylcarbonyl]-β-alanine methyl ester
 IR (Film): 3320, 3000, 2940, 2860, 1730, 1640 cm⁻¹

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NMR (CDCl₃, §): 1.40-2:01 (9H, m), 2.21-2.36 (1H, m), 2.53 (2H, t, J=5.9Hz), 3.13-3.34 (3H, m), 3.48-3.61 (3H, m), 3.70 (3H, s), 3.97-4.00 (3H, m), 4.11-4.41 (3H, m), 5.12 (2H, s), 6.20-6.30 and 6.42-6.51 (total lH, m), 7.30-7.37 (5H, m)

(5) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-piperidyl)proipionyl}-3-piperidylcarbonyl]-3(S)-(4-

Mass (m/z): 490 $(M^{+}+1)$

programmethoxyphenethyl)aminocarbonyl-6-alanine benzyl ester mp : 143°C

2

IR (Nujol) : 3280, 1735, 1680, 1635 cm⁻¹

NMR (CDCl₃, 6): 0.98-1.26 (3H, m), 1.34-1.84 (9H, m), 1.45 (9H, s), 2.19-2.36 (3H, m), 2.52-2.82 (6H, m), 3.01-3.28 (1H, m), 3.39-3.64 (3H, m), 3.78 (3H, s), 4.01-4.44 (3H, m), 4.76-4.86 (1H, m), 5.17 (2H, s), 5.64-5.72 (1/3H, m), 6.00-6.07 (2/3H, m), 6.83 (2H, d, J=8.6Hz), 6.86-7.20 (3H, m), 7.34 (5H, s)

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Mass (m/z): 607 $(M^++1-Boc)$

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 IR (Film) : 3450, 33i7, J80, 2930, 2860, 1720, Je

1640 cm⁻¹

NMR (CDCl₃, 6): 1.01-1.20 (2H, m), 1.22-1.30 (3H, m), 1.45 (9H, s), 1.45-2 05 (13H, m), 2.28-2.72 (8H, m), 3.26=3.59 (2H, m), 3.91-4.48 (4H, m),

4.11 (2H, q, J=7.1Hz), 6.40 (1/3H, d, J=9.0Hz), 6.76 (2/3H, d, J=8.8Hz), 7.16-7.31 (5H, m)

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Mass (m/z) : 572 (M⁺+1)

(7) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4piperidyl)propionyl}-3-piperidylcarbonyl]-β-alanine

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benzyl ester
IR (Film) : 2910, 2840, 1720, 1630 cm⁻¹
NMR (CDCl₃, \(\varepsilon\) : 1.01-1.22 (3H, m), 1.45 (9H, s),
1.33-2.00 (6H, m), 2.18-2.35 (3H, m), 2.54-2.73
(5H, m), 3.15-3.32 (2H, m), 3.45-3.65 (3H, m),
3.81-3.95 (1/2H, m), 4.02-4.19 (3H, m), 4.354.49 (1/2H, m), 5.14 (2H, s), 6.12-6.25 (1/3H, m), 6.54-6.63 (2/3H, m), 7.36 (5H, s)
Mass (m/z) : 530 (M⁺+1)

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(8) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl}-3-piperidylcarbonyl]-\$-alanine 1-cyclohexyloxycarbonyloxy)ethyl ester IR (Film): 2920, 2850, 1740, 1630 cm⁻¹ NWR (DMSO-d₆, §): 1.00-1.83 (13H, m), 1.45 (9H, s), 1.53 (3H, d, J=5.5Hz), 1.89-2.08 (5H, m), 2.02-2.44 (4H, m), 2.52-2.73 (5H, m), 3.11-3.29 (2H, m), 3.39-3.72 (3H, m), 3.88-4.31 (4H, m), 3.87-4.48 (1H, m), 6.30-6.40 (1/3H, m), 6.60-6.69 (2/3H, m), 6.72-6.77 (1H, m)

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(9) N-[(R)-1-{3-(1-text-butoxycarbonyl-4-Fiperidyl)propionÿl-}-3-piperidylcarbonyl]-3(S)phenylsulfonylmethyl-β-alanine text-butyl ester IR (Film): 3300, 1720, 1660, 1620;cm-1.635;vvvvv NWR (CDCl3,-6): 1.08-1.14 (2H, m), 2.20-2.36 (3H, m), 2.67-2.35 (3H, m), 3.27-3.38 (3H, m), 3.60-3.70 (2H, m), 3.86-0.15 (3H, m), 4.48-4.60 (2H, m), 7.58-7.62 (3H, m), 7.90-7.94 (2H, m) Mass (m/z): 650-(M+1)

(10) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-(n-

35

butanesulfonylaminomethyl)~β-alanine tert-butyl ester
IR (Film) : 3280, 1720, 1650, 1620 cm⁻¹

NMR (CDCl₃, δ) : 0.95 (3H, t, J=7.2Hz), 1.18-1.20
(2H, m), 1.45 (18H, s), 1.50-2.10 (15H, m),
2.36-2.40° (3H, m), 2.48-2.72 (4H, m), 2.89-3.05
(3H, m), 3.28-3.35 (2H, m), 3.42-3.55 (1H, m),
3.98-4.24 (3H, m), 4.90-5.10 (1H, m)
Mass (m/z) : 645 (M[†]1)

10 (11) N-(R)-1-(3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(4methoxyphenethyl)-β-alanine methyl ester
IR (Film): 2930, 2860, 1730, 1630 cm⁻¹
NMR (CDCl₃, δ): 1.02-1.21 (2H, m), 1.45 (9H, s),
1.53-1.89 (10H, m), 2.00-2.23 (1H, m), 2.29-2.73 (9H, m), 3.16-3.59 (3H, m), 3.66 (3H, s), 3.78 (3H, s), 3.91 (1H, dd, J=13.8 and 3.6Hz), 4.08 (2H, d, J=12.7Hz), 4.23-4.37 (1H, m), 6.72-6.80 (1H, m), 6.82 (2H, d, J=8.6Hz), 7.09 (2H, d, J=8.6Hz)

Mass (m/z): 588 $(M^{+}+1)$

(12) Ethyl [M-[(R 1-{3-(1-tert-butoxycarbonyl-4-piperidyl pionyl}-3-piperidyl carbonyl]-2-piperidyl carbonyl]-2-piperidyl carbonyl]-2-piperidyl carbonyl]-2-ir [Rilm]: 2980, 2930, 2860, 1720, 1675, 1625 cm-l [Rilm]: 2980, 2930, 2860, 1720, 1675, 1625 cm-l [NMR (CDCl3, 6): 1.00-1.30 (4H, m), 1.45 (9H, s), 1.53-1.87 (14H, m), 2.31-3.28 (11H, m), 3.61-3.89 (2H, m), 4.03-4.16 (4H, m), 4.50-4.69 (2H, m), 4.69-4.75 (1/3H, m), 5.13-5.28 (2/3H, m)]

Mass (m/z): 522 (M+1)

(13) N-[4-{3-(1-tert-butoxycarbonyl-4-piperidyl) propionyl}-2-morpholinylcarbonyl]-6-alanine ethyl

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2.30-2.47 (2H, m), 2.52-2.93 (5H, m), 3.04-3.16 (1H, m), 3.49-3.62 (3H, m), 3.86-4.38 (6H, m), NMR (CDC13, 5): 1.01-1.21 (1H, m), 1.28 (3H, t, J=7.1Hz), 1.45 (9H, m), 1.45-1.73 (6H, m), 4.18 (2H, q, J=7.2Hz), 7.09-7.19 (1H, m) IR (Film) : 2910, 2850, 1720, 1600 cm⁻¹ Mass (m/z): 470 $(M^{+}+1)$ ester

piperidyl)propionyl}-3-piperidylcarbonyl]-3-phenyl-β-(14) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4alanine methyl ester

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NMR (CDCl₃, 6): 0.99-1.24 (2H, m), 1.45 (9H, s), IR (Film): 2940, 2860, 1735, 1630 cm⁻¹

1.45-1.89 (9H, m), 2.00-2.16 (1H, m), 2.25-2.44 3.55 (3H, s), 3.62-4.48 (4H, m), 5.37-5.47 (1H, (3H, m), 2.61-2.96 (4H, m), 3.19-3.55 (2H, m),

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m), 7.28-7.35 (5H, m) Mass (m/z) : 530 (M⁺+1)

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.. Piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(3,4-IB (Zilm) : 3290, 2980; 2925; 2850, 1720, 1650, dimethoxyphenethyl)-8-alanine methyl wster (15) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-1620 cm-1

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1.45-1.94 (9H; m), 2.03-2.73 (11H, m)/3.18-3.67 s), 3.92-4.11 (2H, m), 4.23-4.47 (1H, m), 6.69-(3H, m); 3.66 (3H, s), 3.85 (3H, s), 3.88 (3H, NMR (CDCl3, 6): 1.02-1.23 (3H, m), 1.45 (9H, s),

Mass (m/z) : ~618 (M+1) 6.81 (AH, m)

piperidyl)propionyl}-3-piperidylcarbonyl]-3(\$)hydroxymethyl-β-alanine tert-butyl ester (16) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-

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1.56-1.99 (8H, m), 2.32-2.36 (3H, m), 2.50-2.73 NMR (CDC13, 6): 1.08-1.18 (3H, m), 1.45 (18H, s), (4H, m), 3.00-3.33 (2H, m), 3.52-3.62 (1H, m), 3.69 (3H, t, J=5.2Hz), 4.04-4.20 (4H, m), 6.92 and 7.27 "(total 1H, br)

IR (Film) : 3280, 1640, 1420, 1240, 1150, 860, 740, piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(3methoxyphenethyl)- β -alanine methyl ester (17) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-680 cm-1.

2

1.50-1.96 (бн, т), 2.02-3.10 (16н, т), 3.55 (3н, NMR (DMSO-d₆, 6): 0.80-1.15 (6H, m), 1.38 (9H, s), s), 3.72 (3H, s), 3.95 (2H, m), 4.08-4.22 (1H, m), 6.73 (3H, m), 7.17 (1H, m), 7.84 (1H, m), 8.31 (1H, s)

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Mass (m/z) : 588 $(M^{+}+1)$

1.4.45 7.2 4.24 (1.8H g, m), 1.2:34 - 2.79 (7H, m), 3.35 - 3.50 piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-[2-(3-(1H, m), 3.64 and 3.68 (total 1H, s), 3.91-4.11 ;(2H, m), 4.37 (1H, br), 6.67-6.71 (1H, m), 7.01 NMR DC13, 6): 1.08-1.14 (1H, m), 1.42 (9H, s), (1H, s), 7.04-7.26 (2H, m), 7.32-7.37 (1H, m), 7.56-7.60 (Н, m), 8.14-8,20 (1Н, m) IR (Film) : 3450, 1710, 1660, 1610 cm-1 (18) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4indolyl)ethyl]- β -alanine methyl ester Mass (m/z) : r

piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(3-NWR (CDCl3, 6): 1.00-1.21 (2H, m), 1.45 (9H, s), trifluoromethylphenethyl)-eta-alanine methyl ester IR (Film): 2980, 2925, 2860, 1720, 1645 cm⁻¹ (19) N-[(R)-1-{3-(1:tert-butoxycarbonyl-4-

 $(M^{+}+1)$

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1.45-1.72 (9H, m), 1.84-2.20 (3H, m), 2.34-2.77 3.80-3.81 (1H, m), 4.02-4.17 (2H, m), 4.25-4.39 (9H, m), 3.39-3.50 (1H, m), 3.63-3.69 (4H, m), (1H, m), 6.45-6.53 (1/3H, m), 6.89-6.93 (2/3H, m), 7.35-7.43 (4H, m) Mass (m/z): 626 $(M^{+}+1)$

(20) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-

1.53-2.15 (11H, m), 2.21-2.38 (3H, m), 2.48-2.66 IR (Film) : 2990, 2930, 2860, 1725, 1660, 1620 cm-1 6.64 (lH, d, J≈8.6Hz), 6.81-6.91 (2H, m), 7.09-(6H, m), 3.15-3.60 (2H, m), 3.65 (3H, s), 3.81 (3H, s), 3.86-4.50 (4H, m), 6.23-6.35 (1H, m), NMR (CDCl3, 8): 1.00-1.21 (2H, m), 1.45 (9H, s), piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(2methoxyphenethyl)- β -alanine methyl ester Mass (m/z) : 588 (M+1) 7.19 (2H, m) 10 13

1.56 (2H, d, J=7.4Hz), 1.45-2.11 (8H, m), 2.34piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(3,4-2.73 (10H, m), 3.16-3.60 (3H, m), 3.66 (3H, s), 3.91 (1H, dd, J=13.7 and 3.5Hz), 4.02-4.15 (2H, "m", 4-20-4-34 (1H, m), 5.91 (2H, s), 6.59-6.74 NMR (CDC13, 6): 1.00-1.2; (2H, m), 1.45 (9H, s), IR (Film) : 2980, 2925, 2860, 1725, 1630 cm-1. methylenedioxyphenethyl) $-\beta$ -alanine methyl ester (21) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-(3H, m), 6.79 (1H, d, J=8.7Hz) Mass (m/z): 602 (M^++1) 20

piperidyl)propionyl}-3-piperidylcarbonylj-3(S)-vinyl-IR (Film): 3300, 1720, 1680, 1630, 1530 cm-1 (22) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-B-alanine ethyl ester

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5.12-5.24 (2H, m), 5.76-5.92 (1H, m), 6.64-6.68, 2.33-2.41 (3H, m), 2.55-2.73 (4H, m), 3.27-3.54 (2H, m), 4.07-4.18 (5H, m), 4.62-4.90 (1H, m), NMR (CDCl3, 6): 1.03-1.21 (2H, m), 1.26 (3H, t, J=7.2Hz), 1.45 (9H, s), 1.52-2.05 (10H, m), 6.88-6.92 (total 1H, m) Mass (m/z): 494 (M⁺+1)

J=7.2Hz), 1.50 (9H, s), 1.52-2.03 (9H, m), 1.98 3.21-3.62 (2H, m), 4.07-4.23 (5H, m), 5.08-5.12 (1H, s),2.28-2.40 (4H, m), 2.62-2.73 (4H, m), NMR (CDCl₃, 5) : 1.00-1.21 (2H, m), 1.28 (3H, t, piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-IR (Film) : 3250, 1730, 1670, 1630, 1610 cm⁻¹ (1H, m), 7.06 and 7.28 (total 1H, br) (23) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4ethynyl-ß-alanine ethyl ester

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1.51-1.71 (7H, m), 1.84-2.04 (2H, m), 2.20-2.40 IR (Film) : 3020, 2910, 2840, 1720, 1640, 1620 cm⁻¹ 3.54-3.91 (1H, m), 3.97-4.44 (5H, m), 4.79 (1H, (4H, m), 2.60-3.10 (5H, m), 3.16-3.36 (2H, m), NWR (CDCl₃, 6): 0:98-1.19 (2H, m), 1.45 (9H, s), q, J=6.4Hz), 5.14 (2H, s), 6.81-6.89 (1H, m), piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)propargylaminocarbonyl-\$-alanine benzyl ester (24) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-7.35 (5H, s)

NMR (CDC13, 6): 1.8-1.18 (2H, m), 1.26-1.33 (3H, t, piperidyl)propionyl}-3-pyrrolidinylcarbonyl]-3(S)-IR (Film) : 3280, 1730, 1670; 1630, 1530 cm-1 4.) N-[1-{3-(1-tert-butoxycarbonyl-4ethynyl-ß-alanine ethyl ester

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Mass (m/z): 611 $(M^{+}+1)$

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J=7.4Hz), 1:45 (9H, S), 1.59-1.69 (2H, m), 1.64 3.44-3.76 (4H, m), 4.15-4.19 (2H, m), 4.22 (2H, (3H, s), 2.09-2.31 (5H, m), 2.61-2.96 (5H, m), q, J=7.4Hz), 5.05-5.12 (1H, m), 6.50-6.70 (1H, Ê

piperidyl)propionyl}-3-piperidylcarbonyl]-2-methyl-β-NMR (CDCl₃, 6): 1.08-1.45 (4H, m), 1.52 (9H, s), (26) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-IR (Film): 3260, 1720 cm⁻¹ alanine methyl ester

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1.60-1.63 (7H, m), 1.92-1.97 (2H, m), 2.25-2.39

(3H, m), 2.62-2.73 (3H, m), 3.24-3.56 (5H, m),

3.71 (3H, s), 3.56-3.70 (iH, m), 4.05-4.11 (3H, m), 6.42-6.58 (1H, m) Mass (m/z): 468 $(M^{+}+1)$

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....JEZ.1Hz), 1.45 (9H, s), 1.40-1.80 (7H, m), 1.88-(3H, m), 2.61-2.74 (6H, m), 3.33 (1H, dd, J=13.6 piperidyl)propionyl}-3-piperidylcarbonyl}-3-ethynyl-2.32-2.46 (14, d, J=2.4Hz), 2.38-2.46 J=7.1Hz), 5.03-5.14 (1H, m), 6.68-7.02 (1H, m) and 9.2Hz), 4.02-4.14 (3H, m), 4.19 (2H, G, NMR (CDCl3, 6): 1.01 1.21 (2H, m), 1.28 (3H, IR (Film) : 2980, 2930, 2860, 1730, 1640 cm⁻¹ (27) N-[(S)-1-{3-(1-tert-butoxycarbonyl-4-Mass (m/z) : 492/(M++1) - 2010 B-alanine ethyl ester

(28) 4-[3-{3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl-1.53-1.92 (9H, m), 2.23 (2H, q, J=7.0Hz), 2.36-IR (Film) : 2970, 2920, 2850, 1725, 1650, 1630 cm⁻¹ amino}-1-piperidyl]-4-oxo-butyric acid methyl ester 2.99 (6H; m); 3.15-3.59 (3H; m); 3.69 (3H, s), NMR (CDC13, 8): 0.98-1.21 (2H, m), 1.45 (9H, s),

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'n,

3.74-3.92 (lH, m), 4:00-4.13 (3H, m), 6.09 and 6.24 (total 1H, d, J=6.5 and 7.6Hz) Mass (m/z): 354 $(M^++1-Boc)$

m), 2.45-2.74 (4H, m), 2.88-3.58 (3H, m), 3.73-1.44 (9H, s), 1.52-2.05 (9H, m), 2.14-2.33 (2H, benzyloxycarbonylaminobutyric acid tert-butyl ester 4.48 (5H, m), 4.81-5.19 (3H, m), 6.75-6.79 and NMR (CDCl3, 6): 0.97-1.19 (2H, m), 1.43 (9H, s), piperidyl)propionylamino}piperidyl]-4-oxo-2(S)-IR (Film) : 2950, 2900, 2850, 1700, 1640 cm⁻¹ 6.76-6.82 (total 1H, m), 7.34 (5H, s) (29) 4-[3-{3-(1-tert-butoxycarbonyl-4-Mass (m/z) : 645 $(M^{+}+1)$

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J=7.1Hz), 1.45 (9H, s), 1.54-1.74 (10H, m), 2.06 3.25-3.38 (2H, m), 3.82-3.90 (1H, m), 4.03-4.26 (3H, s), 2.25-2.47 (4H, m), 2.62-2.74 (2H, m), [(6H.j.m.) , 4.72-4.76 (1H, m) , 7.1937 268 (1H, m) NMR (CDCl3, 8): 1.08-1.13 (2H, m), 1.28 (3H, t, piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-(30) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-IR (Film): 3300, 1730, 1660 cm-1 acetylamino-β-alanine ethyl ester Mess (m/z) : 525 (M+1)

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piperidyl)propionyl}-?-piperidy1carbonyl]-2-piperidyl (31) Ethyl N-[(R)-1-{3-(1-tert-butoxycarbonyl-4carboxylate

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2.25-2.39 (2H, m), 2.53-3.14 (8H, m), 3.32-4.08 q, J=7.1Hz), 4.16.4.37 (2H, NMAR (DMSO-d6, 6): 0.82-1.09 (2H, m), 1.17 (3H, J=7:1Hz), 1.38 (9H, s), 1.31-1.99 (11H, m), (6H, m), 4.03 (2H,

. Mass (m/z) : - 508 (M+1)

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piperidyl)propionyl}-3-piperidylcarbonyl]-2-benzyl-β-(32) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4alanine ethyl ester

1.38-1.89°(11H, m), 2.26-2.37 (2H, m), 2.52-3.29 NMR (DMSO-d6, 6): 0.84-1.21 (5H, m), 1.38 (9H, s), (9H, m), 3.68-4.08 (4H, m), 4.13-4.41 (1H, m), 7.14-7.31 (5Н, т), 7.95-8.12 (1Н, т) Mass (m/z) : 558 (M⁺+1)

J=7.1Hz), 1.38 (9H, s), 1.38-1.86 (9H, m), 1.99piperidyl)propionyl}-3-piperidylcarbonyl]-2-phenyl-ß-2.43 (3H, m), 2.51-3.08 (4H, m), 3.33-4.34 (9H, NMR (DMSO-d6, 8): 0.85-1.07 (2H, m), 1.14 (3H, t, m), 7.28-7.38 (5H, m), 7.96-8.12 (1H, m) (33) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4alanine ethyl ester

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Example 2

Mass (m/z): 544 (M^++1)

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stiring at ambient temperature for overnight, the mixture dimethylformamide (12.27.ml) under stirring at 0°C. After by chromatography on silica gel eluting with (CHCl3:MeOH = MgSO4, and evaporated in vacuo. The residue was purified acid (5.02 g) and 1-hydroxybenztriazole (1.69 g) in N,N-(1) To a mixture of 2(S)-(tert-butoxycarbonyl)amino- β -The extract was washed with water, brine and dried over was poured into water and extracted with ethyl acetate. carbonyl-4-piperidyl)propionyl]-3-piperidinecarboxylic NMR (CDC13, 6): 1.04-1.34 (6H, m), 1.47 (9H, s), Piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-(tertalanine ethyl ester (2.89 g), (R)-1-[3-(1-benzyloxy-IR (Film) : 2970, 2930, 2850, 1720, 1680 cm⁻¹ butoxycarbonyl)amino- β -alanine ethyl ester (6.0 g) 100:1) to give N-[(R)-1-{3-(1-benzyloxycarbonyl-4-20

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s), 5.86-5.96 and 7.09-7.17 (total 1H, m), 7.32-3.91-4.25 (6H, m), 4.33-4.45 (1H, m), 5.12 (2H, (2H, m), 3.18-3.40 (2H, m), 3.46-3.60 (2H, m), 7.36 (5H, m)

Mass (m/z): $617 (M^++1)$

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The following compounds were obtained according to a similar manner to that of Example 2 (1).

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m), 3.83-4.01 (1/2H, m), 4.10-4.50 (4h, m), 5.12 3-piperidylcarbonyl]-3-methyl-ß-alanine methyl ester IR (Film) : 3050, 2930, 2850, 1730, 1680, 1635 cm-1 (2) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-NMR (CDC13, 6): 1.02-1.30 (5H, m), 1.40-2.69 (14H, m), 2.76 (2H, t, J=12.9Hz), 3.19-3.68 (5+1/2H, (2h, s), 6.30-6.39 (1/3H, m), 6.50-6.54 (1/3H, m), 6.68-6.72 (1/3H, m), 7.30-7.37 (5H, m) Mass (m/z): 502 (M^++1)

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4.37 (3H, m), 5.12 (2H, s), 6.30-6.38 (1/3H, m), IR (Film) : 3300, 2940, 2870, 1720, 1680, 1649 cm-1 3.69-3.96 (3H, m), 4.15 (2H, q, J=7.1Hz), 4.17-J=6.0Hz), 3.05-3.31 (4H, m), 3.47-3.63 (3H, m), acetyl}-3-piperidylcarbonyl]- β -alanine ethyl ester NMH (CDCl3, 6): 1.27 (3H, t, J=7.1Hz), 1.43-1.96 (3) N-[(R)-1-{2-(1-benzyloxycarbonyl-4-piperidyloxy)-(6H; m), 2.19-2.34 (1H, m), 2.51 (2H, t, 6.51-6.59 (2/3Н, т), 7.30-7.37 (5Н, т) Mass (m/z): 504 (M⁺+1)

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(4) N-[(R)-1-{2-(1-benzyloxycarbonyl-4-piperidyloxy)acetyl}-3-piperioylcarbonyij-3-ethynyl-\$-alanine ethyl ester

NMR (CDCl₃, 6): 1.28 (3H, t, J=7.1Hz), 1.45-1.97 IR (Film): 2930, 2860, 1720, 1640 cm-1

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1:47-1.81 (9H, m), 2:18-2.49 (3H, m), 2:70-2:82

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J=1.5Hz), 2.70 (2H, t, J=5.7Hz), 3.13-3.29 (4H, m), 3.54-3.64 (iH, m), 3.75-4.04 (3H, m), 4.07-4.37 (5H, m), 5.03-5.12 (1H, m), 5.12 (2H, s), (8H, m), 2.23-2.38 (1H, m), 2.27 (1H, d, 6.66-6.97 (1H, m), 7.30-7.36 (5H, m) Mass (m/z): 528 (M^++1)

J=7.1Hz), 4.14-4.37 (3H, m), 5.12 (2H, s), 6.23-IR (Film) : 3305, 2940, 2860, 1720, 1680, 1640 $m cm^{-1}$ 2.51 (2H, t, J=5.9Hz), 3.06-3.31 (4H, m), 3.47-(4H, m), 1.76-1.97 (4H, m), 2.19-2.34 (1H, m), 6.34 (1/3H, m), 6.44-6.53 (2/3H, m), 7.32-7.37 acetyl}-3-piperidylcarbonyl}- β -alanine ethyl ester NMR (CDCl3, 6): 1.27 (3H, t, J=7.1Hz), 1.41-1.68 3.61 (3H, m), 3.70-4.00 (3H, m), 4.15 (2H, q, (5) N-[(S)-1-{2-(1-benzyloxycarbonyl-4-piperidyloxy)-(5H, m)

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Mass (m/z) : 504 (M^++1)

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piperidyl)propionyl}-3-piperidylcarbonyl]-2(R)-tert-IR (F11m) : 3000, 2970, 2930, 2850, 1740, 1680, butoxycarbonylamino-\$-alanine methyl ester 1650, 1630 cm.1 N-[(R)-1-{3-(1-benzyloxycarbonyl-4-A (9)

6.44-5.51 and 6.74-6.81 (total lH, m), 7.30-7.37 1.53-2.05 (9H, m), 2.20-2.44 (3H, m), 2.60-2.84 (2H, m), 3.19-3.61 (4H, m), 3.75 (3H, s), 3.85-4.47 (5H; m), 5.12 (2H, s); 5.51-5.67 (1H, m), NMAR (CDCL3) (5) 3 1:03-1.24 (2H, m), 1.44 (9H, s), (5H, m)

Mass (m/z) : -603 (M++1)

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Example 3

(1) To a mixture of N-[(3-piperidyl)carbonyl]-\$-alanine methyl ester hydrochloride (1.57 g), 3-(1-tert-

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by chromatography on silica gel eluting with (CHCl $_3$:MeOH = $iperidyl)propionyl}-3-piperidylcarbonyl]-\beta-alanine methyl$ MgSO4, and evaporated in vacuo. The residue was purified 1-hydroxybenztriazole (0.96 g) in N,N-dimethylformamide The extract was washed with water, brine and dried over stirring at ambient temperature for 1 hour, the mixture was poured into water and extracted with ethyl acetate. butoxycarbonyl-4-piperidyl)propionic acid (1.61 g) and (16 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.14 ml) under stirring at 0°C. After 100:1) to give N-[1-{3-(1-tert-butoxycarbonyl-4ester as an oil (2.19 g).

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IR (Film): 3410, 3280, 3070, 2910, 2850, 1725, 1680, 1630 cm⁻¹

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1.45-2.05 (10H; m), 2.23-2.39 (3H, m), 2.49-2.73 (4H, m), 3.18-3.64 (4H, m), 3.32 (3H, s), 3.81-4.23 and 4.36-4.49 (total 3H, m), 6.23-6.35 and NMR (CDCl3, 6): 1.03-1.21 (2H, m), 1.45 (9H, s), 6.52-6.62 (total 1H, m)

Mass (m/z): 454 (M^++1) .

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The following compounds were obtained according to similar manner to that of Example 3 (1)

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IR (Nujol) : 3290, 3100, 1740, 1690. 1640, 1615 cm-1 1.52-1.77. (7H, m), 1.77-1.92 (2H, m), 2.23-2.38 3.71 (3H, s), 3.82-3.95 (1H, m), 4.02-4.15 (2H, (3H, m), 2.54 (2H, t, J=5.8Hz), 2.62-2.73 (3H, NMR (CDC13, 5): 1.00-1.20 (2H, m), 1.45 (9H, S), m), 2.99-3.10 (1H, m), 3.52 (2H, q, J=5.8Hz), propiony1:-4-piperidy1carbony1]- β -alanine methy1 m), 4.53-4.67 (1H, m), 6.20-6.29 (1H, m) (2) N-[1-{3-(1-text-butoxycarbonyl-4-piperidyl)-2°67 .∵. din ester

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 $propionyl\} \hbox{$-4-piperidyl}] \hbox{$-\beta-alanine methyl ester}$ (3) N-[2-[1-{3-(1-tert-butoxycarbonyl-4-piperidyl)-IR (Film) : 3300, 1730, 1660 cm-1

1.52-1.76 (9H, m), 2.05-2.07 (2H, m), 2.29-2.37 3.48-3.57 (2H, m), 3.71 (3H, s), 3.78-3.82 (1H, m), 4.04-4.08 (2H, m), 4.58-4.64 (1H, m), 6.04-(2H, m), 2.52-2.73 (4H, m), 2.96-3.01 (1H, m), NMR (CDCl3, 8): 1.08-1.14 (4H, m), 1.45 (9H, s), 6.08 (1H, m)

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Mass (m/z): 468 (M^++1)

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Propionyl}-3-piperidylcarbonyl]-N-methyl- β -alanine (4) N-[1-{3-(1-tert-butoxycarbonyl-4-piperidyl)methyl ester

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1.50-1.87 (10H, m), 2.36-2.45 (2H, m), 2.53-2.72 IR (Film) : 3450, 2900, 1720, 1670, 1650, 1620 cm-1 (3H, m), 3.80-3.88 (1H, m), 4.05-4.60 (2H, m), NMR (CDC13, 6): 1.08-1.36 (2H, m), 1.45 (9H, s), (6H, m), 2.91, 3.11 (total 3H, s), 3.60-3.70 4.,60-4.66 (1H, m)

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Mass (m/z) : 458 -(M⁺)

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. 'm), 1.45 (9H, s), 2.13-2.19 (1/2H, m), 2.25 (2H, NMR (CDCl3, 6): 1.03-1.30 (3H, m), 1.30-2.11 (12H, J=1.5Hz), 4.31-4.44 (1/2H, m), 6.07-6.17 (1/2H, (1/2H, m), 3.48-3.57 (2+1/2H, m), 3.70 (3H, d, acety] -3-piperidyl acety] - B-alanine methyl ester (2+1/2H, m), 3.05-3.15 (1/2H, m), 3.23-3.36 (5) N-R2-[1-(2-(I-tert-butoxycarbony1-4-piperidy1)-IR (Film) : 3300, 2920, 2850, 1730, 1630 cm-1 d, J=6.5Hz), 2.52-2.60 (2H, m), 2.64-2.81 いいかいかられるちゃちんなり m), 6.59-6.69 (1/2H, m)

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Mass (m/z): 454 (M+1)

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(6) N-[1-{4-(1-tert-butoxycarbonyl-4-piperidyl)butyryl}-1.53-2.30 (9H, m), 2.31-2.54 (3H, m), 2.61-2.75 (2H, m), 3.44-3.55 (1H, m), 3.73 (3H, s), 3.78-4.20 and 4.37-4.52 (total 7H, m), 6.25-6.35 and NMR (CDCl₃, 6): 0.99-1.36 (4H, m), 1.45 (9H, s), 3-piperidylcarbonyl]glycine methyl ester IR (Film): 3280, 2910, 2650, 1740 cm-1 6.96-7.04 (total 1H, m) Mass (m/z) : 454 (M+1)

(7) N-[2-[1-{2-(1-text-butoxycarbonyl-4-piperidylidene)acetyl}-3-piperidyl]acetyl]- β -alanine methyl ester mp: 121°C

4.29-4.42 (1/2H, m), 5.86 (1H, s), 6.10-6.23 and 1.80-2.11 (4H, m), 2.25 (2H, t, J=5.0Hz), 2.46 (2H, t, J=5.7Hz), 2.56 (2H, q, J=6.3Hz), 2.74-NMR (CDC13, 8): 1.15-1.80 (3H, m), 1.47 (9H, s), (6+1/2H, m), 3.70 (3H, s), 3.82-3.96 (1H, m), 2.87 (1H, m), 3.10-3.40 (1H, m), 3.43-3.55 IR (Nujol): 3320, 1735, 1680, 1630 cm⁻¹ 6.65-6.80 (total 1H, m)

Mass (m/z): 452 (M+1)

1.53-1.99 (9H, m), 2.31-2 48 (4H, m), 2.60-2.76 3.69 (3H; s), 4.0: 4.11 (2H; m), 5.70-5.93 (1H, IR (Film) : 2960, 2920, 2750, 1725, 1650, 1620 cm-1 propionyl}-3-piperidyl]succ.n ...c acid methyl ester (4H, m), 3.04-3,44 (2H, m), 3.60-3.95 (3H, m), NMR (CDC13, S): 1.00-1.21 (2H, m), 1.45 (9H, S), (8) N-[1-{3-(1-tert-butoxycarbolyi-4-riperidyl)-

Mass (m/z): 454 (M+1)

propionyl}-3-piperidyl]acetyl]glycine methyl ester (9) N-: --[1-{3-(1-benzyloxycarbonyl-4-piperidyl)-

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(3H, s), 3.82-3.95 (1/2H, m), 4.01-4.29 (4H, m), MMR (CDC13, 6): 1.01-1.80 (10H, m), 1.80-2.43 (6H, m), 2.63-2.88:(3H; m), 3.37-3.69 (2H, m), 3.75 (1/2H, m), 6.99-7.08 (1/2H, m), 7.30-7.37 (5H, 4.29-4.42 (1/2H, m), 5.12 (2H, s), 6.01-6.10 IR (Film) : 2920, 2850, 1740, 1675, 1615 cm-1

Mass (m/z) : 488 $(M^{+}+1)$

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(10) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-IR (Film) : 3300, 2930, 2860, 1735, 1680, 1635 cm⁻¹ 3-piperidyl]-2(S)-(tert-butoxycarbonylamino)succinamic acid ethyl ester

J=7.1Hz), 1.45 (9H, S), 1.49-1.98 (9H, m), 2.30-2.40 (2H, m), 2.68-2.84 (4H, m), 2.96-3.17 (1H, s), 5.58-5.74 (1H, m), 5.83-5.96 (1H, m), 7.35m), 3.35-3.53 (1H, m), 362-4.23 (5H, m), 4.21 (2H, q, J=7.1Hz), 4.43-4.54 (1H, m), 5.12 (2H, NMR (CDC13, 5): 1:01-1.27 (2H, m), 1.27 (3H, t, 7.37 (5H, m)

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(11) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-Mass (m/z) : .617 (M+1)

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1.52-1,78 (11H, m); 2:30-2.40 (2H, m), 2.60-3.39 IR (Film) : 3000, 2940 2860 1720, 1680, 1640 cm-1 (2H, s), 5.62-5.75 and 6.55-6.69 (total 1H, m), (6H, m), 3.70 (3H, d, J=2.6Hz), 3.64-3.95 (2H, m), 4.11-4.23 (2H, m), 4:38-4.49 (1H, m), 5.12 NAR (CDC13, S) : 1.03-1:24 (2H, m), 1.46 (9H, s), 3-piperidy1]-3(S)-(tert-butoxycarbonylamino)succinamic acid methyl ester was observed and

Mass (m/z) : 503 (M⁺+1)

7.35-7.37 (5H, m)

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(12) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl-3-

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piperidyl]-3(R)-(tert-butöxycarbonylamino)succinamic acid ethyl ester

IR (Film) : 2960, 2910, 2840, 1710, 1680, 1660,

1640 cm⁻¹

J=7.9Hz), 2.59-3.52 (6H, m), 3.65-3.98 (3H, m), 4.14 (2H, q, J=7.1Hz), 4.09-4.20 (2H, m), 4.39-4.49 (1H, m), 5.12 (2H, s), 5.62-5.76 (1H, m), (CDCl₃, 6): 1.03-1.26 (3H, t, J=7.1Hz), 1.46 (9H, s), 1.46-1.98 (9H, m), 2.35 (2H, t, 6.59-6.61 (1H, m), 7.29-7.37 (5H, m) MAR

Mass (m/z): 617 $(M^{+}+1)$

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Example 4

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and tetrahydrofuran (3 ml) was hydrogenated at atmospheric piperidylcarbonyl]-2(S)-benzoylamino-eta-alanine ethyl ester dissolved in N,N-dimethylformamide (5 ml), and 1-ethyl-3-(230 mg) and 10% Pd-C (50 mg, 50% wet) in ethanol (5 ml) water and extracted with ethyl acetate. The extract was pressure for 1 hour. After the catalyst was removed by residue, 3-(1-tert-butoxycarbonyl-4-piperidyl)propionic che mixture vas poured into (3-dimethylaminopropyl)carhodiimide (97 µl) was added chromatography on silica gel eluting with (CHCl3:MeOH NMR (CDCl3, 6): 0.85-1.33 (2H, m), 1.29 (3H, t, 100 :1) to give N (R)-1-{3-(1-text-outoxycarbonyl-4benzoylamino-eta-alanine ethyl ester as an oil (213 mg). filtration, the filtrate was concentrated in vacuo. acid (123 mg) and 1-hydroxybenztriazole (65 mg) was IR (Film) : 2960; 2920, 2850, 1730, 1650 cm-1 washed with water, brine and dried over MgSO $_4$, and (1) A mixture of N-[(R)-3-(1-benzyloxycarbonyl)computeristining at 0°C. After stirring at ambient evaporated in vacuo. The residue was purified by $piperidyl)propionyl}-3-piperidyl;arbonyl]-2(S)...$: so temperature for overnig?

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J=7.1Hz), 1.45 (9H, s), 1.45-2.12 (9H, m), 2.20-

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m), 4.80-4.96 (1H, m), 7.39-7.48 (3H, m), 7.51-2.70 (7H, m), 3.14-3:79 (4H, m), 3.97-4.30 (5H, 7.60 (2/3H, m), 7.8-7.84 (1/3H, m), 7.96-8.04

Mass (m/z): '587 (M++1)

The following compounds were obtained according to a similar manner to that of Example 4 (1)

1.45-1.89 (13H, m), 1.27-2.51 (4H, m), 2.61-2.73 3.60-3.75 (IH, m), 4.01-4.30 (7H, m), 6.18 (1H, (2H, m), 2.97-3.05 (2H, m), 3.25-3.40 (2H, m), NMR (CDCl₃, 6): 0.94 (3H, t, J=7.3Hz), 1.02-1.38 piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-(n-(2H, m), 1.30 (3H, t, J=7.1Hz), 1.45 (9H, s), butanesulfonylamino)-\$-alanine ethyl ester IR (Film) : 2910, 2850, 1720, 1630 cm⁻¹ (2) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4d, J=8.9Hz), 7.35-7.42 (1H, m) Mass (m/z): 603 (M^++1) 10 12 20

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(3H, m), 146 (9H, s), 1.46-1.77 (9Hp/m), 2.24-1900 100 2050 (4H, m), 2056-2.78 (2H, m); 3.17-3.34 (2H, NMR (CDCl₃, 6): 1.14 (2H, t, J=7.1H2), 1.08-1.17 m), 3.58-3.73 (1H, m), 3.87-4.23 (7H, m), 6.48 (1H, d, J=9.3Hz), 7.19-7.27 (1H, m), 7.45-7.56 piperidyl)propionyl}-3-piperidylcarbonyl]=2(S)phenyisulfonylamino- β -alanine ethyl-ester IR (Film): 3400, 1720, 1645, 1620 cm⁻¹ (3) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-(3H, m), 7/81-7.88 (2H, m) Mass (m/z): 623 $(M^{+}+1)$

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Example 5

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To a solution of 3-(1-benzyloxycarbunyl-4-

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Piperidyl)propionic acid (0.18.g) in N,N-dimethylformamide (CHCl₃:MeOH = 100:1) to give $N-[1-{3-(1-benzyloxycarbonyl-}]$ was purified by chromatography on silica gel eluting with solution saturated NaHCO3 aqueous solution and brine, and tetrahydrofuran (2 ml) was added. After stirring at $0^{\circ}\mathrm{C}$ isobutylchloroformate (0.1 ml) under stirring at -15°C. dried over MgSO $_4$, and evaporated in vacuo. The residue mixture was poured into water, and extracted with ethyl for 2 hours and ambient temperature for overnight, the quinolylcarbonyl]- β -alanine ethyl ester as an oil (0.18 The extract was washed with 5% ${
m KHSO}_4$ agueous tetrahydro-3-quinolyl)carbonyl]- β -alanine ethyl ester (3 ml) was added N-methylmorpholine (0.09 ml) and After stirring at -15°C for 2 hours, N-[(1,2,3,4-(0.22 g) and N-methylmorpholine (0.12 ml) in 4-piperidyl)propionyl}-1,2,3,4-tetrahydro-3-

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J=7.1Hz), 1.54-1.65 (4H, m), 2.48-2.56 (4H, m), 2.65-2.83 (3H, m), 2.95-3.07 (2H, m), 3.53 (2H, q, J=6.0Hz), 3.72-3.87 (1H, m), 4.05-4.21 (4H, m), 4.16 (2H, q, J≂7.2Hz), 5.10 (2H, s), 6.60-NMR (CDCl3, 6): 1.01-1.14 (2H, m), 1.27 (3H, t, 6.67 (1H, m), 7.00-7.36 (9H, m) Mass n/:) : 550 (M++1)

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concentrated in vacuo. The residue was purified by column 1-hydroxybenztriazole (209 mg) in N,N-dimethylformamide (4 piperidyl)propionyl]-3-piperidine]carboxylic acid (571 mg) chromatography on cilica gel eluting with (CHCl $_3$:MeOH $_=$ A solution of N-fluorenylmethoxycarbonyl-3-amino-To a mixture of 212 mg of this 3(S)-cyanopropionic acid tert-butyl ester (0.3 g) in diethylamine (6 ml) was stirred for 1 hour, and oil, (R)-1-[3-(tert-butoxycarbonyl)-4-100:3) to give an oil.

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ml) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (283 ambient temperature for overnight, the mixture was poured into water and extracted with ethyl acetate. The extract μ l) were added under stirring at 0°C. After stirring at chromatography on silica gel eluting with (CHCl $_3$:MeOH = piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-cyano-βwas washed with water, brine and dried over MgSO4, and 100:1) to give N-[(R)-1-{3-(1-tert-butoxycarbonyl-4evaporated in vacuo. The residue was purified by alanine tert-butyl ester (0.4 g).

1.49 (9H, s), 1.54-2.09 (10H, m), 2.32-2.39 (3H, 3.23-3.62 (3H, m), 4.00-4.14 (2H, m), 5.12-5.22 IR (Film) : 2980, 2930, 2860, 2250, 1720, 1640 $m cm^{-1}$ m), 2.61-2.79 (2H, m), 2.74 (2H, d, J=5.6Hz), NMR (CDCl3, 6): 1.05-1.25 (2H, m), 1.45 (9H, s), (1H, m), 7.51 (1h, d, J-8.4Hz) Mass (m/z): 521 (M+1)

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Example 7

stirring at ambient temperature for 2 hours, the sesulting (1) To a solution of $N-[(R)-1-\{3-(1-benzyloxycarbonyl-4$ precipitates were collected by filtration to give N-(R)-"Promy ethyl ecetate. (60 ml) was added a solution of .4N HCl in butoxycarbonyl)amino-ß-alanine ethyl ester (5.98 g) in ethyl acetate (24.2 ml) under stirring at 0°C. After piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-(tert-1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-3piperidylcarbonyl]-2(S)-amino- β -alanine ethyl ester ydrochloride (3.41 g), 20 25

(13H, m), 2.11-2.43 (3H, m), 2.57-3.17 (4H, m), 3.46-4.38 (4H, m), 5.06 (7H, s), 7.28-7.42 (5H, NMR (DMSO-d₆, 5): 0.89-1.10 (2H, m), 1.19-1.91 IR (Nujol): 1745, 1695, 1650 cm⁻¹

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Mass (m/z): 517 (M+1) free of compound

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The following compounds were obtained according to a similar manner to that of Example 7 (1). (2) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl-3-2.69-3.06 (7H, m), 3.51-3.87 (2H, m), 3.94-4.05 NMR (DMSO-d6, 6): 1.17 (3H, t, J=7.1Hz), 1.33-1.51 (1H, m), 4.12-4.29 (4H, m), 5.06 (2H, s), 7.30-(6H, m), 1.60-1.84 (5H, m), 2.22-2.37 (2H, m), piperidyl]-2(\ddot{s})-aminosuccinamic acid ethyl ester Mass (m/z): 517 (M^++1) free of compound 7.42 (5H, m), 8.27-8.43 (1H, m) IR (Nujol) : 1730, 1640 cm-1 hydrochloride

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piperidyl)propionyl}-3-piperidylcarbonyl]-2(R)-amino-B-alanine methyl ester hydrochloride (3) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-IR (Nujol): 1740, 1640 cm-1

(13H, m), 2.11-2.43 (4H, m), 2.61-3.17 (6H, m), 3.45-4.46 (5H, m), 5.06 (2H, s), 7.30-7.42 (5H, NMR (DMSO-d6, 6): 0.90-1.09 (2H, m), 1.21-1.91 m), 8 5ù-8.59 (1H, m)

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... Mass (m/z) : 503 (M+1) tree of compound 4) N-1-{3-(1-benzyloxycarbonv1.:-piperidyl)-propionyl}-3-piperidyl] =3(S)-aminosuccinamic acid methyl ester hydrochloride

mp : 75°C

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3.49-3.74 (2H, m), 3.91-4.09 (4H, m), 5.06 (2H, (11H, m), 2.20-2.38 (2H, m), 2.60-3.25 (7H, m), NMR (DMSO-d6, 6): 0.90-1.09 (2H, in), 1.31-1.88 ER (Nujol): 1725, 1670, 1640, 1650.cm-1 s), 7.35 (5H, s), 8.66-8.84 (1H, m)

Mass (m/z): 503 (M^++1) free of compound

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N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-3-piperidyl]-3(R)-aminosuccinamic acid ethyl ester hydrochloride (2)

IR (KBr, pellet) : 2939, 2864, 1732, 1684, 1616 cm⁻¹ J=7.0Hz), 5.06 (2H, s), 7.30-7.42 (5H, m), 8.64-2.20-2.39 (2H, m), 2.60-3.26 (6H, m), 3.51-3.73 J=7.0Hz), 1.37-1.53 (6H, m), 1.60-1.86 (4H, m), NMR (DMSO-d6, 8): 0.90-1.09 (2H, m), 1.20 (3H, t, (2H, m), 3.88-4.28 (3H, m), 4.09 (2H, g, 8.75 (1H, m)

Mass (m/z): 517 (M^++1) free of compound

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Example 8

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carbonyl-4-piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-(1) To a solution of N-[(R)-1-{3-(1-benzyloxycarbonyl-4and acetyl chloride (38 μ l) under stirring at 0°C. After was poured into water and extracted with dichloromethane. stirring at ambient temperature for 2 hours, the mixture lichloromethane (4 ml) was added triethylamine (150 μ l) aqueous solution, water and brine; and dried over $MgSO_4$, $piperidyl)propionyl\}-3-piperidylcarbonyl\}-2(S)-amino-\beta (CHCl_3:MeOH = 100:1)$ to give $N-[(R)-1-\{3-(1-benzyloxy-1)\}$ and evaporated in vacuo. The residue was purified by acetylamino- β -alanine ethyl ester as an oil (130 mg). IR (Film) : 3290, 3060, 3000, 2930, 2850, 1725, The extract was washed with water, saturated NaHCO3 column chromatography on silica gel eluting with alanine ethyl ester hydrochloride (270 mg) in 1675, 1640 cm⁻¹

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2.31-2.50 (3H, m), 2.70-2.83 (2H, m), 3.16-3.3I 4.70-4.80 (1H, m), 5.12 (2H, m), 7.05-7.22 (1H, (3H, m), 3.64-3.74 (1H, m), 4.05-4.34 (6H, m), MAR (CDCl3, 6): 1.06-1.34 (2H, m), 1.27 (3H, t, J=7.1Hz), 1.41-1.76 (10H, m); 2.09 (3H, s), m), 7.26-7.37 (5H, m)

Mass (m/z) : 559 (M++1)

The following compounds were obtained according to a similar manner to that of Example 8 (1).

propionyl}-3-piperidylcarbonyl]-2(S)-n-hexanoylamino-IR (Film) : 3000, 2940, 2870, 1735, 1655, 1640 cm-1 2.70-2.84 (2H, m), 3.25-3.70 (7H, m), 4.05-4.25 (12H, m), 1.51-1.75 (7H, m), 2.24-2.51 (5H, m), (5H, m), 4.69-4.80 (1H, m), 5.12 (2H, s), 7.03-NMR (CDCl3, 6): 0.89 (3H, t, J=7.1Hz), 1.12-1.38 (2) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-piperidyl)-7.15 (1H, m), 7.30-7.38 (5H, m) β-alanine ethyl ester

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Mass (m/z) : 615 (M+1)

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piperidyl)propionyl}-3-piperidylcarbonyl}-2(S)-(4-IR (Film): 3000, 2930, 2860, 1740, 1680, 1650, chlorobenzoylamino)-β-alanine ethyl ester (3) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-1600 cm⁻¹

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J=7.1Hz), 1.29-1.80 (11:(, m), 2.20-2.55 (3H, m), m), 7.41 (2H, d, J=8.6Hz), 8.00 (2H, d, J=8.6Hz) 2.65-2.80 (2H, m), 3.12-3.28 (2H, m), 3=32-3.42 4.90-4.98 (1H, m), 5.12 (2H, s), 7.35-7.43 (6H, (1H, m), 3.61-3.79 (1H, m), 4.07-1.42 (5H, m), NMR (CDCl3, 5): 0.89-1.1; (2H, m), 1.29 (3H, t, Mass (m/z): 655 (M^++1)

J=7.1Hz), 2.26-2.56 (3H, m), 2.64-2.80 (2H, m), NMR (CDC13, 8): 0.84-1.80 (13H, m), 1.29 (3H, t, piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-4-IR (Film): 2920, 1730, 1685, 1630, 1600 cm-1 methoxybenzoylamino-\b-alanine ethyl ester (4) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-

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5.87-5.97 (total 6H, m), 5.11 (2H, s), 5.92 (2H, 3.15-3.86 (3H, m), 3.83 (3H, s), 4.05-4.38 and d, J=8.8Hz), 7.33-7.45 (6H, m), 7.75-7.81 (1H, m), 8.00 (2H, d, J=8.8Hz)

Mass (m/z) : 651 (M⁺+1)

(5) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-3-piperidyl]-2(S)-benzoylaminosuccinamic acid ethyl

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2.64-3.13 (5H, m), 3.34-4.00 (4H, m), 4.08-4.28 J=7.1Hz), 1.38-1.97 (8H, m), 2.22-2.40 (2H, m), m), 5.12 (2H, s), 5.86-6.00 (1H, m), 7.28-7.36 (2H, m), 4.26 (2H, q, J=7.1Hz), 4.91-5.01 (1H, (5H, m), 7.41-7.56 (4H, m), 7.78-7.87 (2H, m) NMR (CDC13, 6): 1.03-1.33 (3H, m), 1.29 (3H, t, IR (Film) : 2920, 1730, 1680, 1640 cm⁻¹ Mass (m/z) : $621 \cdot (M^{+}+1)$

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J=7:1Hz), 1.40-1.80 (11H, m), 2.31-2.54 (3H, m), 2.68-2.88 (2H, m), 3.20-3.40 (2H, m), 3.62-3.75 5.12 (2H, s), 6.70-6.80 and 7.08-7.15 (total 1H, (1H, m), 4.08-4.32 (6H, m), 4.72-4.81 (1H, m), IR (Film): 3000, 2930, 2860, 1730, 1650 cm⁻¹
NER (CDC13, 6): 0.73-1.37 (6H, m), 1.27 (3H, t, piperidyl)propionyl}-3-piperidylcarbonyl]-2(S) $cyclopropylcarbonylamino-\beta-alanine$ ethyl ester (6) N-[(R)-1-{3-(1-benzyloxycarbonyl-4m), 7.21-7.48 (6H, m)

Mass (m/z) : . 585 (M+1)

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propionyl}-3-piperidylcarbonyl]-2(R)-benzoylamino- β -(7) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-piperidyl)alanine methyl ester

IR (Film) : 3060, 3010, 2960, 2860, 1740, 1690, 1640, 1610 cm⁻¹

and 4.33-4.44 (total 4H, m), 3.77 (3H, s), 4.10-2.62-2.83 (2H, m), 3.36-3.45 (2H, m), 3.62-3.80 7.29-7.59 (9H, m), 7.81-7.89 (2H, m), 8.04-8.09 NMR (CDC13, 8): 0.99-1.21 (2H, m), 1.32-1.87 (8H, 4.22 (2H; m), 4.70-4.86 (1H, m), 5.11 (2H, s), m), 2.03-2.48 (2H, m), 2.33 (2H, t, J≂7.7Hz), (1H, m)

607 (M⁺+1) Mass (m/z) :

(8) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-3-piperidyl]-3(S)-benzoylaminosuccinamic acid methyl

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m), 2.16-2.40 (2H, m), 2.66-2.83 (3H, m), 3.01-4.89-5.00 (1H, m), 5.12 (2H, s), 6.88-7.20 (1H, m), 7.31-7.37 (5H, m), 7.43-7.56 (3H, m), 7.78-IR (Film) : 3000, 2940, 2860, 1735, 1680, 1640 cm⁻¹ NMR (CDC13, 6): 0.98-1.24 (2H; m), 1.34-1.95 (9H, 4.00 (6H, m), 4.15 (3H, s), 4.07-4.23 (2H, m), 7.89 (3H, m)

Mass (m/z) : 607 (M^++1)

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(9) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-3-piperidy]]-2(S)-acetylaminosuccinamic acid ethyl ester

Ik (Film) : 3050, 2990, 2920, 2850, 1725,81650, 1620 cm⁻¹ NMR (CDC13, 6): 1.04-1.24 (2H, m), 1.27-1.28 (total J=7.1Hz), 4.71-4.82 (1H, m), 5.12 (2H, s), 6.02 s), 2.31-2.41 (2H, m), 2.69-3.16 (5H, m), 3.34and 5.09 (total 1H, d, J=7.1Hz), 6.71-6.88 (1H, 4.05 (4H, m), 4.11-4.24 (2H, m), 4.22 (2H, g, 3H, t, J=7.1Hz), 1.41-1.99 (9H, 13), 2.03 (3H, m), 7.30-7.37 (5H, m)

Mass (m/z) : 559 (M⁺+1)

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(10) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-}
piperidyl)propionyl}-3-piperidylcarbonyl]-2(R)acetylamino-β-alanine methyl ester
IR (Film) : 2940, 2850, 1740, 1650 cm⁻¹
NMR (CDCl3, 6) : 1.03-1.28 (2H, m), 1.40-1.79 (9H, m), 2.03 (3H, s), 2.20-2.40 (3H, m), 2.64-2.84 (2H, m), 3.20-3.69 (5H, m), 3.75 (3H, s), 3.82-3.89 (1H, m), 4.11-4.23 (2H, m), 4.55-4.68 (1H, m), 5.12 (2H, s), 7.00-7.09 (2H, m), 7.27-7.37

Mass (m/z): 545 $(M^{+}+1)$

(5H, m)

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Mass (m/z) :: mi624.4(Mth.) #Hessis : :

(12):4-{3-{1-tert-butoxycarbony1-4-

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Piperidyl)propionylamino}-1-piperidyl]-4-oxo-2(S)
"benzoylaminobutyric acid tert-butyl ester

IR (Film) :: 3050, 2970, 2930, 2850, 1750, 1640 cm⁻¹

NGR (CDCl₃, §) : 0.94-1.20 (2H, m), 1.45-1.79 (10H, m), 1.45 (9H, s), 1.46 (9H, s), 2.12-2.39 (7H, m), 2.52-2.80 (3H, m), 3.87-4.36 (4H, m), 7.31-

9

Mass (m/z) .: 615 $(M^{+}+1)$

7.58 (4H, m), 7.75-7.85 (2H, m)

Example 9

'n

(1) To a mixture of N-[(R)-1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-amino-β-alanine ethyl ester hydrochloride (1 g), 3-methoxypropionic ačid (0.17 ml) and 1-hydroxybenztriazole (0.24 g) in N,N-dimethylformamide (10 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.33 ml) under stirring at 0°C. After stirring at ambient temperature for overnight, the mixture was poured into water and extracted with ethyl acetate. The extract washed with water, brine and dried over MgSO₄, and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with (CHCl₃:MeOH = 100:1) to give N-[(R)-1-{3-(1-benzyloxycarbonyl)-4-piperidyl)propionyl)-anino-β-alanine ethyl ester (0.59 g) as an oil.

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IR (Film): 3050, 2980, 2860, 1730, 1660, 1640, 1620 cm⁻¹

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NMR (CDCl₃, 6): 1.05-1.33 (2H, m), 1.28 (3H, t, J=7.2Hz), 1.42-1.82 (14H, m), 2.11-2.61 (4H, m), 2.67-3.84 (2h, m), 3.37 (3H, s), 3.40-3.57 (2H, m), 3.61-3.76 (2H, m), 3.85-4.03 (1H, m), 4.12-4.26 (4H, m), 4.67-4.76 and 6.93-7.05 (total 1. m), 5.12 (2H, s), 7.22-7.39 (6H, m)

Mass (m/z): 603 (M⁺+1)

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The following compounds were obtained according to a similar manner to that of $\underline{\mathtt{Example~9~(1)}}$.

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N-[(R)-1-{3-(1-benzyloxycarbonyl-4-(3)

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J=7.1Hz), 1.34-1.80 (10H, m), 2.29-2.77 (5H, m), 3.13-3.71 (4H, m), 4.02-4.40 (5H, m), 4.93-5.03 (1H, m), 5.09 (2H, s), 7.34 (5H, s), 7.36-7.51 (4H, m), 7.59-7.69 (4H, m), 7.80-7.99 (1H, m), piperidyl)propionyl}-3-piperidylcarbonyl}-2(S)-4-NMR (CDCl₃, 6): 0.90-1.15 (2H, m), 1.30 (3H, t, IR (Film) : 2930, 2850, 1735, 1660, 1640 cm⁻¹ biphenylcarbonylamino- β -alanine ethyl ester 8.11 (2H, d, J=8.4Hz)

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Mass (m/z) : 697 $(M^{+}+1)$

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Example 10

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hydroxide (0.35.g) under stirring at 0°C. After stirring propionyl}-3-piperidylcarbonyl]-3-ethynyl- β -alanine (1.12 (1) A solution of N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-Alanine ethyl ester (43.38.9) in tetrahydrofuran (5 ml), The extract was washed with water, brine and dried over ${\rm MgSO_4}_4$, and evaporated in vacuo to .piperidyl)propionyl)-3-pipgridylcarbonyl3=3-ethynyl-6-, acidified with 5% KHSO $_4$ aqueous solution and extracted give N-[(R)-1-(3-(1-tert-butoxycarbonyl-4-piperidyl)at ambient temperature for 1 hour, the mixture was ethanol (5.ml); and water (5 ml) was added lithium " with ethyl acetate.

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IP: (Nujol) : 3200, 1720, 1630 cm⁻¹

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1.44-2.29 (9H, m), 2.40-2.60 (5H, m), 2.70-3.08 $(DMSO-d_{6}, 6) : 0.68-I.16 (4H, m), 1.21 (9H, s),$ (2H, m), 3.52-4.28 (5H, m), 4.58-4.75 (1H, m), 8:22-8:29 (1H, m), 12:17-12:31 (1H, br)

Mass (m/z) : "464 (M+1)

The following compounds were obtained according to a similar manner to that of Example 10 (1) $(2) (3R)-N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-piperidyl)}-$ 1.40-1.84 (9H, m), 2.03-2.42 (5H, m), 2.55-2.74 IR (Film) : 3410, 2970, 2930, 2880, 1710, 1630 $m cm^{-1}$ NMR (DMSO-d₆, 6): 0.83-1.90 (5H, m), 1.38 (9H, s), (3H, m), 2.87-3.11 (1H, m), 3.69-4.37 (5H, m), propionyl}-3-piperidylcarbonyl]-3-methyl-ß-alanine 7.83 (1H, d, J=8.0Hz) Mass (m/z): 452 $(M^{+}+1)$ 2 15

(3) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-

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1.32-1.83 (9H, m), 2.26-2.40 (5H, m), 2.55-2.75 NMR (DMSO-d₆, 6) : 0.84-1.09 (2H, m), 1.38 (9H, s), piperidyl)propionyl}-3-piperidylcarbonyl]-\b-alanine (3H, m), 2.84-3.27 (3H, m), 3.71-3.°°°(3H, m), 4.11-4.38 (13, m), 7.90-8.02 (1E in) IR (Film): 3400, 2910, 1700, 1630 cm-1 Mass (m/z) : 440 (M++1)

Example 11

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acetylamino-eta-alanine ethyl ester (130 mg) in a mixture of temperature for 1 hove; the mixture was acidified with 10% ethanol (1.5 00) and tetrahydrofuran (0.5 ml) was added a (1) To a solution of N-[(R)-1-{3-(1-benzyloxycarbonyl-4solution of lithium hydroxide (11 mg) in water (1.5 ml) under stirring at 0°C. After stirring at ambient piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-

(10H, m), 1.99 (3H, s), 2.05-2.36 (3H, m), 2.56-IR (Film) : 3810, 3000, 2950, 2880, 1730, 1655 cm-1 3.51 (6H, m), 3.74-3.83 (1H, m), 3.94-4.04 (2H, KHSO4 aqueous solution and extracted with ethyl acetate. m), 4.16-4.40 (2H, m), 5.06 (2H, s), 7.30-7.37 The extract was washed with water, brine and dried over carbonyl]-2(S)-acetylamino- β -alanine as an oil (67 mg). MgSO4 and evaporated in vacuo to give $N-[(R)-1-\{3-(1$ benzyloxycarbonyl-4-piperidyl)propionyl}-3-piperidyl-NMR (DMSO-d6, 6): 0.80-1.09 (2H, m), 1.24-1.80 (5H, m), 7.95-8.09 (2H, m) Mass (m/z): 531 (M^++1)

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The following compounds were obtained according to a similar manner to that of Example 11 (1).

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3.95-4.23 (1H, m), 6.94-7.09.(5H, m), 7.65 (1H, NMR (DMSO-d₆, 6): 0.63-0.86 (2H, m), 1.17 (9H, s), 1.17-1.29 (8H, m), 1.26-1.66 (5H, m), 2.04-2.18 (4H, m), 2.30-2,54 (5H, m), 3.49-3.90 (4H, m), piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-IR (Film) : 3400, 2920, 2850, 1700, 1640 cm-1 AND DESCRIPTION OF THE PARTY OF (2) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-phenethyl-ß-alanine d, J=8Hz)..

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3.57-3.70 (2H, m), 4.03-4.26 (3H, m), 4.77-4.88 J=6.6Hz), 2.49-2.74 (1H, m), 2.84-3.21 (6H, m), NMR (DMSO-d6, 6): 1.22-2.36 (8H, m), 2.59 (1H, d, IR (Film) : 3360, 2940, 1760, 1710, 1625 cm-lpiperidylcarbonyl]-3(S)-ethynyl-ß-alanine (3) N-[(R)-1-{2-(4-piperidyloxy)acety1}-3 $\frac{1}{2}$ $[\alpha]_{60}^{0} = -19.11^{\circ}, (C=1.0, MeOH)$ trifluoroacetate.

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Mass (m/z): 366 (M^++1) free of compound (4H, m), 8.31-8.43 (2H, m)

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piperidylcarbönyl]-3(R)-ethynyl-ß-alanine $N-[(R)-1-\{2-(4-piperidyloxy)acetyl\}-3$ trifluoroacetate

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NMR (DMSO-d6, 6) : 1.20-2.00 (6H, m), 2.11-2.76 (3H, 3.95-4.32 (8H, m), 4.75-4.89 (1H, m), 8.42 (2H, m), 2.58 (1H, d, J=7.4Hz), 2.86-3.23 (6H, m), IR (Film) : 3250, 2920, 1710, 1625 cm⁻¹ t, J=8.6Hz)

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Mass (m/z) : 366 (M^++1) free of compound

(11H, m), 1.38 (9H, s), 2.25-2.40 (3H, m), 2.55-IR (Film) : 3410, 2930, 2850, 1710, 1680, 1610 cm-1 3.14 (9H, m), 3.68-3.97 (4H, m), 4.27-4.39 (2H, m), 4.45-4.58 (1/3H, m), 4.88-5.03 (2/3H, m) NMR (DMSO-d6, 5): 0.83-1.07 (3H, m), 1.34-1.71 piperidyl)propionyl}-3-piperidylcarbonyl[-2-(4) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-Mass (m/z) : 494 (M⁺+1) Piperidylacetic acid 15 20

NMR (DMSO-d6, 6): 0.83-1.06 (2H, m), 1.25-1.44 (4H, 3.39-3.98 (6H, m), 4.08-4.59 (2H, m), 7.45-7.56 m), 1.38 (9H, s), 1.54-1.86 (5H, m), 2.15-2.33 (3h, m), 2.56-2.73 (2H, m), 2.90-3:10 (1H, m), (3H, m), 7.83-7.87 (2H, m), 8.13.8.23 (1H, m), piperidyl)propionyl}-?-piperidylcarbonyl]-2(S)-IR (Film) : 2930, 1720, 1650, 1635 cm⁻¹ (5) N-[(R)-1-{3-(1-tert-butox carbonyl-4-Mass (m/z): 559 $(M^{+}+1)$ benzoylamino-β-alanine 8.60-8.66 (1H, m) 30

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IR (Nujol) : 3370, 3250, 3180, 1700, 1685, 1640 cm⁻¹ 7.95-8.06 (1H, m), 8.16 (1H, t, J=8:6Hz), 12.66-WR (DMSO-d6, 6): 0.80-1.06 (2H, m), 1.14-1.43 (6H, 3.23-3.40 (2H, m), 3.71-3.97 (4H, m), 4.14-4.40 m), 1.38 (9H, B), 1.55-1.71 (3H, m), 1.88-2.34 (3H, m), 2.42-2.71 (2H, m), 2.83-3.14 (2H, m), (1H, m), 7.50-7.68 (3H, m), 7.75-7.79 (2H, m), piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-(6) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4phenylsulfonylamino-β-alanine 12.80 (1H, br)

Mass (m/z); 595 (M⁺+1)

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(1H, m), 8.02-8.11 (1H, m), 12.93-13.00 (1H, br) 3.77-4.01 (4H, m), 4.19-4.42 (1H, m), 7.50-7.57 NMR (DMSO- d_6 , 6) : 0.87 (3H, t, J=7.3Hz), 0.84-1.07 (2H, m), 1.30-1.46 (7H, m), 1.38 (9H, s), 1.57-1.90 (7H, m), 2.29-2.36 (2H, m), 2.55-2.75 (3H, m), 2.85-3.50 (3H, m), 2.96 (2H, t, J=7.7Hz), piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-n-IR (Nujol): 3330, 3250, 1715, 1690, 1640 (7) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-Mass (m/z) : ...475 (Mt+1-Boc) butansulfonylamino-\b-alanine

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2.13-2.64 (8H, m), 2.89-3.06 (1H, m), 3.17-3.28 WMR (DMSO-d6, 8): 0.92-1.17 (2H, m), 1.38 (9H, s), (1H, m), 3.76-4.32 (3H, m), 4.78-4.84 (1H, m), 1.49-1.77 (9H, m), 1.91, 1.99 (total IH, s), piperidyl)propionyi,-3-piperidylcarbonyl]-3(S)-IR (KBr) : 3430, 3300, 1731, 1686, 1662 cm⁻¹ (8) N-[(R)-1-{3-(1-tert-butoxycarbonyl+4-378) aV 8.37-8.44 (1H, m), 12.39 (1H, br) .. ethynyl-ß-alanine

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piperidyl)propionyl}-3-piperidylcarbonyl}-3(S)-(9) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-IR (Film): 3380, 1710, 1640 cm-1 propargylaminocarbonyl-\b-alanine

1.42-1.91 (8H, m), 2.26-2.37 (3H, m), 2.54-2.76 4.08-4.37 (1H, m), 4.46-4.57 (1H, m), 7.18-7.33 NWR (DMSO-d₆, °6) : 0.85-1.08 (2H, m), 1.38 (9H, s), (6H, m), 2.88-3.12 (2H, m), 3.69-3.98 (5H, m), (1H, m), 8.08-8.18 (1H, m), 8.31-8.36 (1H, m)

Mass (m/z): 521 (M+1)

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NMR (DMSO-d₆, 6) : 0.85-1.10 (2H, m), 1.38 (9H, s), 1.21-1.86 (8H, m), 2.08-2.40 (3H, m), 2.56-2.71 (4H, m), 2.87-3.12 (3H, m), 3.21 (1H, dd, J=5.4 propionyl}-3-piperidylcarbonyl}-3-ethynyl-\b-alanine and 2.3Hz), 3.71-4.43 (4H, m), 4.74-4.87 (1H, m), 8.39-8.46 (1H, m), 12.40-12.50 (1H, br) (10) N-[$(S)-1-\{3-(1-\text{tert-butoxycarbonyl-4-piperidyl})-$ IR (Film): 3000, 2930, 2870, 1720, 1640 cm⁻¹

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Mass (m/z): 464 (M^++1)

 $piperidyloxy) \\ \texttt{e.etyl} \\ \texttt{-} \\ \texttt{-} \\ \texttt{piperidylcarbonyl} \\ \texttt{]} \\ \texttt{-} \\ \texttt{\beta-} \\ \texttt{alanine} \\$ THE IR. (Film) : AMAGE 1720, 1720, 1620 cm-1 [11] N-[(S)-1-{2-(1-benzyloxycarbonyl-4-

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., : 1.32-1.91 (8H, m), 2.06 2.30 (1H, 2.85-3.29 (5H, m), 3.47-3.79 (4H, m), 4.01-4.33 (3H, m), 5.06 (2H, s), 7.30-7.37.(5H, m), 7.93m), 2.56 (2H, t, 3=6.9Hz), 2.57-2.71 (1H, m), 8.01 (1H, br); 12.15-12.30 (1H, br) NMR (DMSO-d

Mass (m/z): 476 (N+1)

piperidyl)propionyl}-3-piperidylcarbonyl}-2(S)-(4-IR (Film) : 3400, 1720, 1635, 1600 cm-1 (12) N-[(R)-1-{3-(1-benzyloxycarbonyl)-4chlorobenzoyl)amino-ß-alanine 35

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MMR (DMSO-d₆, 5): 0.87-1.19 (2H, m), 1.31-1.44 (3H, m), 1.53-1.85 (4H, m), 2.12-2.34 (2H, m), 2.59-2.83 (11H, m), 3.93-4.05 (2H, m), 4.14-4.58 (1H, m), 5.05 (2H, s), 7.29-7.40 (5H, m), 7.57 (2H, d, J=8.5Hz), 7.82-7.89 (2H, m), 8.11-8.20 (1H, m), 8.66-8.74 (1H, m)

Mass (m/z): 627 (M⁺+1)

(13) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-(4-methoxybenzoylamino)-β-alanine
IR (Film): 3350, 2920, 1715, 1630, 1600 cm⁻¹
NMR (DMSO-d₆, S): 0.85-1.84 (12H, m), 2.07-2.44
(3H, m), 2.56-3.23 (5H, m), 3.37-3.75 (2H, m), 3.81 (3H, s), 3.91-4.08 (2H, m), 4.14-4.56 (1H, m), 5.05 (2H, s), 7.01 (2H, d, J=8.8Hz), 7.30-7.37 (5H, m), 7.83 (2H, d, J=8.7Hz), 8.11-8.19 (1H, m), 8.42-8.49 (1H, m), 12.68-12.75 (1H, br)
Mass (m/z): 623 (M⁺+1)

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(14) N-[1-{3-(1-benzyloxycarbonyl)-4-piperidyl)propionyl}-3-piperidyl]-2(S)-benzoylaminosuccinamic acid
IR (Film) :-03250; 2900, 1710, 1635 cm⁻¹
NMR (DMSO-d₆, E₁ = ''0.84-1.05 (2H, m), 1.31-1.47 (5H, m), 1.57-1.83 (4H, m), 2.15-2.35 (2H, m), 2.62-2.82 (4H, m), 2.94-3.09 (2H, m), 3.50-3.82 (3H, m), 3.90-4.03,(2H, m), 4.69-4.81 (1H, m), 7.5.05 (2H, E), 7.33-7140 (5H, m), 7.44-7.57 (3H, m), 7.83-8.05 (3H, m), 8.58-8.68 (1H, m)
Mass (m/z) : 593 (M*+1)

(15) N-[(R)-1-{3-(1-benzyloxycarbonyl-4 piperidyl)propionyl}-3-piperidylcarbonyl]-2(S) cyclopropylcarbonylamino-β-alanine
 IR (Film): 3300, 3000, 2930, 2860, 1720; 1640 cm⁻¹

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NMR (DMSO-d₆, δ): 0.66 (4H, d, J=6.5Hz), 0.89-1.10 (2H, m), 1.21-1.87 (10H, m), 2.07-2.37 (3H, m), 2.58-3.55 (6H, m), 3.71-3.84 (1H, m), 3.94-4.05 (2H, m), 4.17-4.40 (2H, m), 5.06 (2H, s), 7.35-7.39 (5H, m), 7.96-8.06 (1H, m), 8.24-8.31 (1H, m), 12.63-12.71 (1H, br)

Mass (m/z): 557 (M⁺+1)

(16) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-piperidylCarbonyl]-2(S)-(3-methoxypropionyl)-3-piperidylCarbonyl]-2(S)-(3-methoxypropionyl)amino-6-alanine

IR (Film): 3480, 2920, 1710, 1640 cm⁻¹

NMR (DMSO-d₆, 6): 0.94-1.29 (2H, m), 1.37-1.84

(11H, m), 2.06-2.40 (2H, m), 2.36 (2H, t, J=6.5Hz), 2.56-3.04 (3H, m), 3.20 (3H, s), 3.36-3.55 (2H, m), 3.51 (2H, t, J=6.5Hz), 3.73-3.83

(1H, m), 3.94-4.06 (2H, m), 4.18-4.39 (2H, m), 5.05 (2H, s), 7.35 (5H, s), 7.90-8.09 (2H, m)

Mass (m/z): 575 (M⁺+1)

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(17) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-Piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-(4hydroxybenz6yl)amino-β-alanine .A (Nujol) : 3250p-1720, 1630, 1600 cm⁻¹ NMF (DMSO-d6r.6) : 0.89-1.85 (12H, m), 2.11-2.34 (.A', m), 2.51-3.09 (4H, m), 3.45-3.84 (2H, m), 3.95-4.05 (2H, m), 4.12-4.54 (2H, m), 5.06 (2H, Si, 6.82 (A', d, J=6.8Hz), 7.30-7.39 (5H, m), 1.72 (2H, d, J=7.2Hz), 8.10-8.19 (1H, m), 8.32-8.39 (1H, m), 10.02 (1H, S), 12.65-12.74 (1H, br) (18) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl {-3-piperidyl}-2(5) acetylaminosuccinamic acid

Mass (m/z) : 609 (M⁺+1)

NMR (DMSO-d₆, 6) : 0.90-1.12 (2H, m), 1.29-1.52 (5H, 3.94-4.05 (3H, m), 4.39-4.59 (1H, m), 5.05 (2H, m), 1.61-1.80 (4H; m), 1.82 (3H, s), 1.92-2.36 (2H, m), 2.44-3.08 (5H, m), 3.17-3.87 (3H, m), s), 7.23-7.39 (6H, m), 7.76-8.13 (1H, m) IR (Film) : 3270, 2900, 1720, 1640 cm-1 Mass (m/z): 531 (M^++1) (19) N-[1-{3-(1-benzyloxycarbonyl)-4-piperidyl)propionyl}-NMR (DMSO-d6, 8): 0.85-1.05 (2H, m), 1.22-1.50 (5H, m), 1.54-1.83 (4H, m), 2.11-2.35 (2H, m), 2.55-2.83 (4H, m), 2.90-3.06 (2H, m), 3.17-3.76 (3H, (2H, s), 7.33 (5H, s), 7.40-7.54 (3H, m), 7.82-7.90 (2H, m), 7.92-8.11 (1H, m), 8.60-8.69 (1H, m), 3.88-4.05 (2H, m), 4.67-4.80 (1H, m), 5.05 IR (Film) : 3280, 2910, 2850, 1715, 1640 cm^{-1} 3-piperidy1]-3(R)-benzoylaminosuccinamic acid

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piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-(4-(20) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-Mass (m/z) : 593 $(M^{+}+1)$

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... biphenylcarbonylamino-β-alanine

NMR (DMSO-d6, 6): 0.86-1.05 (2H, m), 1.11-1.45 (4H, m), 1.54-1.88 (6H, m), 2.05-2:34 (3H, m), 2.58-Sedandar ope IR (Film) : 3300, 2940, 1730, 3690, 1660, 1640 cm-1 m), 7.72-7.82 (4H, m), 7:93+7.99 (2H, m), 8.14-3.11 (3H, m), 3.23-3.80 (4H, m), 3.90-4.57 (3H, m), 5:05 (2H, 8)7 7:34 (5H, 8), 7:40-7:55 (3H, 8.23 (lH, m), 8.64-8.71 (lH, m)

Mass (m/z) : 669 (M⁺+1)

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(21) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-piperidyl) propionyl}-3-piperidylcarbonyl}-2(S)-(nhexanoy1)amino- β -alanine "

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NMR (DMSO-d₆, δ): 0.85 (3H, t, J=6.6Hz), 0.90-1.09 2.09 (2H, t, J=7.4Hz), 2.28-2.36 (2H, m), 2.57-IR (Film): 3350, 3000, 2930, 2860, 1700, 1640 cm-1 (2H, m), 1.14-1.29 (5H, m), 1.39-1.85 (10H, m), 3.54 (7H, m), 3.71-3.84 (1H, m), 3.94-4.06 (2H, m), 4.17-4.40 (2H, m), 5.06 (2H, s), 7.30-7.42 (5H, m), 7.90-8.03 (2H, m) Mass (m/z) : 587 (M+1)

NMR (DMSO-d₆, 6): 0.83-1.09 (2H, m), 1.38 (9H, s), 1.38-1.80 (9H, m), 1.84 (3H, s), 2.07-2.39 (3H, m), 2.51-3.22 (6H, m), 3.73-4.40 (5H, m), 7.96piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-IR (Film) : 3280, 2960, 2920, 1720, 1650 cm⁻¹ (22) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-Mass (m/z): 497 $(M^{+}+1)$ acetylamino-β-alanine 8.10 (2H, m) 10 12

Example 12 20

piperidyloxy)acetyl}-3-piperidylcarbonyl]- β -alanine methyl NMR (DMSO-d6, F): 1.25-1.90 (8H, m), 2.09-2.31 (1H, tetrahydrofuran (10 ml) was added in NaOH (8.55 ml) under 2.85-3.29 (5H, m), 3.50-3.84 (4H, m), 4.10-4.34 stirring at 0°C. After firring at ambient temperature extract was washed with water and brine, and dried over m), 2.36 (2H, t, J=6,9Hz), 2.56-2.70 (1H, m), (1) To a solution of N-[1-{2-(1-benzyloxycarbonyl-4for 3 hours, the mixture was acidified with 10% KHSO $_4$ aqueous solution, and extracted with ethyl acetate. ester (1.33 g) in methanol ($\overline{10}$ ml), H_20 (10 ml) and $MgSO_4$, and evaporated in vacuo to give $N-\{1-\{2\ (1$ piperidylcarbonyl]- β -alanine (1.22 g) as an oil. IR (Film): 3330, 2940, 1700, 1630 cm⁻¹ Denzyloxycarbonyl-4-piperidyloxy)acetyl}-3-

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The following compounds were obtained according to similar manner to that of Example 12 (1).

IR (Film) : 3400, 2920, 2850, 1660, 1640, 1620 cm-1 NMR (DMSO-d6, 6): 0.84-1.50 (7H,), 1.52-1.94 (5H, 2.61-3.03 (4H, m), 3.67-3.88 (1H, m), 3.73 (2H, m), 2.03 (2H, t, J=7.9Hz), 2.22-2.41 (2H, m), d, J=5.3Hz), 3.98-4.28 (3H, m), 5.06 (2H, s), 7.28-7.42 (5H, m), 8.14-8.29 (1H, m), 12.20piperidyl)propionyl}-3-piperidyl]acetyl]glycine (2) N-[2-[1-{3-(1-Benzyloxycarbonyl-4-(m/z): 472 $(M^{+}-1)$ 12.37 (1H, br) Mass

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(3) N-[1-{3-(1-Benzyloxycarbonyl-4-piperidyl)propionyl-3-NMR (DMSO-d6, 6): 0.88-1.13 (5H, m), 1.24-1.51 (4H, m), 1.51-1.83 (5H, m), 2.03-2.43 (5H, m); 2.55-John John St. 1980 (4H. J. 188 - 188 (1H. J. 180 - 4.40 (4H.) 。 1.1 2.5 25 25 25 25 25 25 25 25 (2H, s), 7.35-7.39 (5H, m); 7.83 (3H, IR (Film): 3380, 2910, 2850, 1660, 1615 cm-1 piperidylcarbonyl]-3-methyl-β-alanine Mass (m/z) : 488 (M⁺+1) d, J=7.9Hz) 20

NMR (DMSO-d₆, 6) : 0.85-1.06 (2H, m), 1.43-2.20 (6H, s), 5.53-5.61 (1H, m), 7.09-7.23 (4H, m), 7.30-(4) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}-3.23-3.32 (2H, m), 3.55-3.99 (5H, m), 5.05 (2H, m), 2.39 (2H, t, J=6.9Hz), 2.88-2.84 (4H, m), (1,2,3,4-tetrahydro-3-quinolyl)carbonyl]-A-alamine IR (Film): 3410, 3940, 1760, 1650, 1635 cm-1 The state of the s

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7.42 (5H, m), 8.10-8:18 (1H, m) Mass (m/z): 522 (M+1)

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Example 13

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extracted with ethyl acetate. The extract was washed with water, brine and dried over MgSO $_4$, and evaporated in vacuo $piperidyl) propionyl\}-3-piperidyl carbonyl]-\beta-alanine\ as\ an$ ester (2.03 g) in methanol (10 ml) and water (10 ml) was mixture was acidified with 5% KHSO $_{f q}$ aqueous solution and added lithium hydroxide (0.56 g) under stirring at 0°C . After stirring at ambient temperature for 1 hour, the (1) A solution of 'N-[1-{3-(1-tert-butoxycarbonyl-4to give N-[1-{3-(1-tert-butoxycarbonyl-4oil (1.62 g).

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1.42-1.83 (9H, m), 2.26-2.40 (4H, m), 2.52-2.74 NMR (DMSO-d6, 6): 0.83-1.07 (2H, m), 1.38 (9H, s), (2H, m), 2.87-3.27 (5H, m), 3.70-3.95 (3H, m), 4.16-4.38 (1H, m), 7.92-8.02 (1H, m), 12.05-IR (Film): 3300, 2920, 1715, 1630 cm-1 Mass (m/z): 440 (M^++1) 12.10 (1H, br)

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The following compounds were obtained according to a similar manner to that of Example 13 (1).

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NMR (DMSO-d6, 6): 0.80-1.07 (2H, m), 1.23-1.46 (6H, piperidyl)propionyl}-4-piperidyl.carbonyl]-\b-alanine 3.78-3.99 (3H, m), 4.28-4.40 (1H, m), 7.89 (1H, m), 1.38 (9H, s), 1.55-1.71 (4H, m), 2.27-2.36 (3H, m), 2.36 (2H, t, J=6.9Hz), 2.46-2.75 (2H, m), 2.89-3.05 (1H, m), 3.22 (2H, q, J=5.9Hz), .iR (Film) : 3400, 3050, 2910, 1720, 1610 cm-1 (2) N-[1-{3-(1-tert-butoxycarbonyl-4t, J=5.5Hz)

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Mass (m/z): 438 (M+_1)

MMR (DMSO-d₆, 6) : 0.84-1.10 (2H, m), 1.18-1.29 (2H, 4.12-4.28 and 4.38-4.49 (total lH, m), 8.25 (lH, (3) N-[1-{4-(1-tert-butoxycarbonyl-4-piperidyl)butyryl}m), 1.38 (9H, s), 1.46-1.91 (8H, m), 2.24-2.38 (3H, m), 2.59-3.20 (4H, m), 3.69-4.00 (6H, m), IR (Film) : 3390, 2920, 2850, 1720, 1650 cm⁻¹ 3-piperidylcarbonyl]glycine t, J=5.8Hz)

Mass (m/z): 440 (M^++1)

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piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(4-(4) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4nethoxyphenethyl)- β -alanine

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MAR (DMSO-d6, б) : 0.85-1.09 (2H, m), 1.25-1.49 (4H, (9H, m), 2.89-3.16 (1H, m), 3.71 (3H, s), 3.77m), 1,38 (9H, s), 1.39-1.88 (8H, m), 2.10-2.72 4.06 (4H, m), 4.12-4.39 (1H, m), 6.82 (2H, d, J=8.6Hz), 7.07 (2H, d, J=8.6Hz), 7.83 (1H, d, IR (Film) : 3400, 3930, 3860, 1700, 1630 cm-1 J=8.4Hz), 12.08 (1H, s)

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Mass (m/z) : 574 (M*+1) with the

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○日本のでのできるのです。 「Propionyl{-3-piperidylcarbonyl}-3-phenyl-β-alanine IR (Film) : 3380, 3020, 2940, 2870, 1710, 1660, .. 1630 cm-1 1

NMR (DMSO-d6, 6): 0.86-1.06 (2H, m), 1.21-1.91 (9H, 4.05-4.42 (1H, m), 5:11-5.23 (1H, m), 7.17-7.31 m), 1.38 (9H, s), 2.16-2.35 (3H, m), 2.58-2.67 (5H, m), 2.86-3.06 (1H, m), 3.63-3.97 (3H, m), (5H, m), 8.40-8.47 (1H, m)

Mass (m/z) : ..516 (M⁺+1)

NMR (DMSO-d6, 6) : 0.83-1.10 (2H, m), 1.21-1.46 (4H, (10H, m), 2.87-3.20 (2H, m), 3.70 (3H, s), 3.73 6.74-6.85 (2H, m), 7.83 (1H, d, J=8.2Hz), 11.97. piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(3,4-IR (Film) : 3300, 3430, 3360, 1720, 1640, 1625 cm⁻¹ m), 1.38 (9H, s), 1.61-1.91 (8H, m), 2.07-2.73 (3H, s), 3.76-4.08 (3H, m), 6.64-6.68 (1H, m), (6) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4dimethoxyphenethyl)-\$-alanine Mass (m/z) : 604 (M+1) 12.14 (1H, br) 10

NMR (DMSO-d₆, 8): 0.92-1.12 (2H, m), 1.38 (9H, s), piperidyl)propionyl}-3-piperidylcarbonylj-3(R)-(3-. 1.38-1.98 (13H, m), 2.03-3.20 (14H, m), 3.72 J=6.0Hz), 7.17 (1H, t, J=8.3Hz), 7.84 (1H, d, (3H, s), 3.75-4.38 (6H, m), 6.73 (3H, d, (7) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4methoxyphenethyl)- β -alanine Mass (m/z) : 574 (M^++1) J=8.6Hz) 20

1.30-1.44 (4H, m), 1.59-1.86 (6H, m), 2.28-2.40 WAR (DMSO-d₆, 6): 0.86-1.09 (2H, m), .1.38 (9H, s), 3.71-4.05 (5H, m), 4.15-4.40 (1H, m), 7.48-7.56 (5H, m), 2.60-2.74 (5H, m), 2.82-3.14.(1H, m), piperidyl)propionyl}-3-piperidylcarbonyl}-3(R)-(3-IR (Film): 3280, 2920, 2850, 1720, 1630 cm-1 (8) N-[:R)-1-{3-(1-tert-butoxycarbonyl-4rifluoromethylphenethyl)-\$-alanine (4H, m), 7.85-7.90 (1H, m) Mass (m/z): 612 (M^++1)

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piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(2-(9) N-[(R)-1-{3-(1-tert-butcxycarbonyl-4-

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IR (Film) : 3290, 3000, 2930, 2850, 1715, 1640, methoxyphenethyl)-ß-alanine 1615 cm⁻¹ NMR (DMSO-d6, 5): 0.84-1.08 (2H, m), 1.30-1.45 (4H, (10H, m), 2.89-3.18 (1H, m), 3.71-4.02 (4H, m), 3.75 (3H, s), 4.16-4.39 (1H, m), 6.81-6.94 (2H, m), 1.38 (9H, s), 1.59-1.91 (7H, m), 2.09-2.74 m), 7.07-7.20 (2H, m), 7.84 (1H, d, J=8.5Hz), 12.12 (1H; s)

Mass (m/z) : 574 (M+1)

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piperidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(3,4-IR (Film) : 3380, 2960, 2920, 2860, 1710, 1650, (10) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4 $methylenedioxyphenethyl)-\beta-alanine.$

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NMR (DMSO-d6, 5): 0.86-1.07 (2H, m), 1.24-1.94 (5H, 4.14-4.39 (1H, m), 5.95 (2H, s), 6.59-6.63 (1H, m), 1.38 (9H, s), 1.59-1.87 (7H, m), 2.30-2.70 (9H, m), 2.90-3.15 (1H, m), 3.70-4.00 (4H, m), m), 6.74-6.81 (2H, m), 7.83 (1H, d, J=8.3Hz), 12.09-12.19 (1H, br) 1620 cm-1

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... Mass (m/z) : 588 (M+1)

. piperidyl)propionyl}-3-piperidylcarbonyl]-2(R)-IR (Film): 3260, 2900, 1710, 1630 cm⁻¹ (11) N-[(R)-1-(3-(1-benzyloxycarbonyl-4-· · · benzoylamino-β-alanine

NMR (DMSO-d6, 8) : 0.86-1.04 (2H, m), 1.23-1.45 (4H, m), 1.56-1.83 (5H, m), 2.12-2.36 (3H, m), 2.57-3.81 (7H, m), 3.91-4.04 (2H, m), 4.14-4.62 (2H, m), 5.05.(2H, s), 7.28-7.35 (5H, m), 7.47-7.63 (3H, m), 7.83-7.97 (2H, m), 8.15-8.23 (1H, m), 8.64 (1H, t, J=7.1Hz)

Mass (m/z) : .593 (M+1)

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NMR (DMSO-d6, 6): 0.87-1.06 (2H, m), 1.32-1.83 (9H, (12) N-[1-{3-(1-benzyloxycarbonyl-4-piperidyl)propionyl}m), 2.15=2.35 (3H, m), 2.58-3.07 (8H, m), 3.51-3.79 (2H, m), 3.87-4.03 (2H, m), 4.67-4.80 (1H, m), 5.05 (2h, s), 7.29-7.39 (5H, m), 7.45-7.56 (3H, m), 7.81-7.89 (2H, m), 8.57-8.68 (1H, m) 3-piperidyl]-3(S)-benzoylaminosuccinamic acid IR (Film): 3290, 2930, 1745, 1640 cm-1 Mass (m/z) : 593 (M+1)

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NMR (DMSO-d6, 6): 0.90-1.12 (2H, m), 1.23-1.79 (9H, IR (Film) : 3400, 2930, 2860, 1720, 1655, 1630 cm-1 4.20-4.40 (2H, m), 5.06 (2H, s), 7.28-7.42 (5H, m), 1.84 (3H, s), 2.11-2.40 (4H, m), 2.61-3.48 (5H, m), 3.74-3.88 (1H, m), 3.96-4.08 (2H, m), Piperidyl)propionyl}-3-piperidylcarbonyl]-2(R)-(13) N-[(R)-1-{3-(1-benzyloxycarbonyl-4m), 7.98-8.08 (2H, m) Mass (m/z): 531 (M^++1) acetylamino-β-alanine

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The following compound was obtained according to a similar manner to that of Example 12 (1)

Example 14

NMR (DMSO-d6, 6): 0.87-1.31 (4H, m), 1.38 (9H, s), 1.55-2.66 (9H, m), 2.14-2.28 (2H, m), 2.37 (2H, J=6.0Hz), 3.68-4.27 (4H, m), .91-8.03 (1H, m) t, J=6.8Hz), 2.60-3.02 (4H, m), 3.23 (2H, q, Piperidyl)acetyl}-3-piperidyl]acetyl]-\b-alanine IR (FILM) : 3300, 2920, 2850 1710, 1635 cm-1 (1) N-[2-[1-{2-(1-tert-butoxycarbonyl-4-Mass (m/z): 438 $(M^{+}-1)$

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(2) N-[2-[1-{2-(1-tert-butoxycarbonyl-4-

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piperidylidene)acetyl}-3-piperidyl]acetyl}-ß-alanine 1.57-1.91 (4H, m), 1.96-2.00 (2H, m), 2.14-2.24 NMR (DMSO-d6, 6) : 1.09-1.41 (3H, m), 1.41 (9H, s), 3.71-3.83 (1H, m), 4.02-4.26 (1H, m), 5.90 and (2H, m), 2.28-2.40 (3+1/2H, m), 2.64-2.83 (1H, 5.96 (total 1H, s), 7.69-8.03 (1H, m), 12.17m), 2.91-3.06 (1/2H, m), 3.19-3.46 (5H, m), IR (Film) : 3200, 2925, 1680, 1650 cm⁻¹ 12.24 (1H, br)

1.38-1.85 (11H, m), 1.99-2.11 (2H, m), 2.41-2.43 3.60-3.76 and 4.09-4.20 (total 3H, m), 3.85-3.96 IR (Film) : 3250, 2920, 1710, 1660, 1640, 1620 cm⁻¹ MR (DMSO-d₆, 5) : 0.82-1.04 (2H, m), 1.38 (9H, s), (3H, m), 2.56-2.76 (2H, m), 2.98-3.12 (1H, m), propionylamino}-1-piperidyl]-4-oxo-butyric acid (2H, m), 7:73, 7.84 (total 1H, d, J=8.0 and (3) 4-[3-(1-tert-butoxycarbonyl-4-piperidyl)-6.4Hz), 12.03 (1H, s) Mass (m/z): 440 (M+1)

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piperidyl)propionyl}-2-morpholinylcarbonyl]; \b-alanine IR (Film) : 3400, 2980, 2920, 2880, 1710, 1640 cm-1 1.38-1.49% (3H) m), 3.59-1.70 £(4H, m), 2.29-2.44 NWR (DMSO-d6, 6) & 0184 Fr08 (2H, m), 1.38 (9H, s), (16, m), 2.40 (2H, t, J=7.0Hz), 2.58-2.92 (3H, m), 3.09-3.56 (3H, m), 3.70-3.98 (5+1/2H, m), 4.41-4.51 (1/2H, m), 7.77-7.94 (1H, m) (4) N-[4-{3-(1-text-butoxycarbonyl-4-Mass (m/z): 440 (M⁺-1)

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piperidyl)propionyl}-3-piperidyl)succinamic acid IR (Film): 3400, 1710, 1680, 1630 cm-1 (5) N-[1-{3-(1-tert-Butoxycarbony1-4-

NMR (DMSO-d6, 8): 0.84-1.06 (2H, m), 1.26-1.31 (6H, 3.45-3.76 (2H, m), 3.84-3.96 (2H, m), 7.76-7.92 m), 1.38 (9H, s), 1.59-1.84 (4H, m), 2.20-2.46 (6H, m), 2.57-2.74 (2H, m), 2.91-3.08 (2H, m), (1H, m), 12.00-12.06 (1H, br)

Mass (m/z): 340 $(M^++1-Boc)$

NMR (DMSO-d6, 6): 1.25-2.02 (8H, m), 2.10-2.16 (1H, 2.86-3.25 (7H, m), 3.59-3.72 (2H, m), 4.07-4.31 (3H, m), 7.99 (1H, t, J=5.5Hz), 8.42-8.60 (2H, m), 2.37 (2H, t, J=6.8Hz), 2.55-2.71 (1H, m), IR (Film): 2940, 1760, 1820, 1660, 1630 cm-1 piperidylcarbonyl]- β -alanine trifluoroacetate (6) $N-[(R)-1-\{2-(4-piperidyloxy)acetyl\}-3 [\alpha]_{b}^{20} = 20.07^{\circ} (C=1.0, MeOH)$

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Mass (m/z): 438 (M^++1)

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Mass (m/z): 342 (M^++1) free of compound

Example 15

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□ give N[±][(R).-1-{3-(1= ... hours... After the catalyst was removed by filtration, the piperidylcarbonyl]-3(S).ethyl- β -alanine ethyl ester (0.73 alanine ethyl ester (0.8 g) and PtO₂ (0.2 g) in ethanol A mixture of N-[(R)-1-{3-(1-tert-butoxycarbonyl-4piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-vinyl- β -10 ml) was hydrogenated at atmospheric pressure for 2 tert-butoxycarbonyl-4-piperidyl)propionyl}-3filtrate was concentrated in vacur g) as a colorless oil.

(6H, m), 1.45 (9H, s), 1.52-2.03 (11H, m), 2.33-J=7.5Hz), 3.77-4.17 (5H, m), 6.64-6.69 (1H, br) EMR (CDCl3, 6): 0:92 (3H, t, J=7.5Hz), 1.08-1.30 2.74 (6H, m), 3.26-3.51 (2H, m), 3.72 (2H, q, JX (Film): 3300, 1740, 1620 cm-1

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The solution of 4-[3-(3-(1=tert-butoxycarbony1-4-piperidy1)propionylamino}-1-piperidy1]-4-oxo-2(S)benzyloxycarbonylaminobutyric acid tert-butyl ester (1.35 g) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 10% Pd-C (0.27 g, 50% wet) was hydrogenated at atmospheric pressure for 6 hours. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo to give 4-[3-(3-(1-tert-butoxycarbony1-4-piperidy1)propionylamino}-1-piperidy1]-4-oxo-2(S)-aminobutyric acid tert-butyl ester (1.07 g) as an oil.

IR (Film): 2970, 2930, 2880, 1720, 1650 cm⁻¹

NMR (CDC13, 6): 0.97-1.20 (2H, m), 1.45 (18H, s), 1.33-1.84 (9H, m), 2.15-2.46 (2H, m), 2.53-2.76 (3H, m), 2.85-3.60 (5H, m), 3.70-4.40 (4H, m), 7.35 (1H, s)

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Example 17

Mass (m/z) : 511 (M⁺+1)

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To a mixture of thioanisole (13.7 ml) and m-cresol (12.2 ml) in tetrahydrofuran (150 ml) was added N-[(R)-1-{2-(1-benzyloxycarbonyl-4-piperidyloxy)acetyl}-3-piperidyloxy)acetyl}-3-piperidyloxy)acetyl}-3-thymyl-β-alanine ethyl ester (1.54 ° g). After stirring at ambient temperature for 2 hours, the mixture was poured into water and washed with diethyl ether. The extract was purified by HDLC QN_CLB silica geleluting with (0.1% TFA aqueous solution:CH3CN = 44.1) to give N-[(R)-1-{2-(4-piperidyloxy)acetyl}-3-ethynyl-β-alanine ethyl ester trifluoroacetate as an oll (0.17 g).

NMP. (DMSO-d6, 6): 1.78 and 1.18 (total 3H, t, J=7.1 and 7.0Hz), 1.29-2.71 (10H, m), 2.65 (1H, d, J=7.2Hz); 2.90-3.2 (5H, m), 3.57-3.63 (3H, m), 4.01-4.39 (7H, m), 4.80-4.90 (1H, m), 8.45-8.56 (1H, m)

Mass (m/z): 394 (M^++1) free of compound

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Example 18

A mixture of N-[(R)-1-(3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-(4-methoxyphenethylamino)carbonyl- β -alanine benzyl ester (0.9 g) and 10% Pd-C (0.2 g, 50% wet) in acetic acid (10 ml) was hydrogenated at atmospheric pressure for 3 hours. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was poured into water and extract with ethyl acetate. The extract washed with water, brine and dried over MgSO4, and evaporated in vacuo. To give N-[(R)-1-(3-(1-tert-butoxycarbonyl)-4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-(4-methoxyphenethylamino)carbonyl- β -alanine as an oil (0.79 g).

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IR (Film): 3390, 2930, 1710, 1645 cm⁻¹

NMR (DMSO-d₆, δ): 0.80-1.10 (3H, m), 1.30-1.84 (9H, m), 1.38 (9H, s), 1.91-1.99 (2H, m), 2.15-2.40 (3H, m), 2.58-2.69 (4H, m), 2.88-3.26 (5H, m), 3.71 (3H, s), 3.76-4.53 (3H, m), 6.84 (2H, d, J=8.4Hz), 7.11 (2H, d, J=8.3Hz), 7.93-8.02 (1H, m), 8.09-8.18 (1H, m), 12.11-12.28 (1H, br)

Mass (m/z): 617 (M⁺+1)

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Example 19

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(1) Thionyl chlor (0.05 ml) was added to ethanol (1 ml) under stirring at -10°C. After stirring at -10°C for 10 minutes, N-[(R)-1-{3-(4-piparidyl)propionyl}-3-piperidylcarbonyl]-3(R)-(3_methoxyphenethyl)-\$\beta\$-alanine hydrochloride (100 mg) was added. The mixture was stirred at ambient temperature for 2 hours, and evaporated in vacuo. The residue was dissolved in water and desalted by HP-20 eluting with (IPA:water = 1:1) to give N-[(R)-1-{3-methoxyphenethyl-\$\beta\$-alanine ethyl ester (80 mg).

NAR (DMSO-d6, 6): 1.15 (3H, t, J=7.1Hz), 1.19-1.93

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3.96-4.05 (5Н, m), 4.12-4.39 (1Н, m), 6.72-6.75 (12H, m), 2.10-3.19 (14H, m), 3.72 (3H, s), (3H, m), 7.14-7.22 (1H, m), 7.89 (1H, d, J=8.2Hz)

Mass (m/z) : $502 (M^{+}+1)$

The following compound was obtained according to similar manner to that of Example 19 (1)

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(3H, m), 2.60-3.29 (7H, m), 3.16 (3H, s), 3.59-3.84 (2H, m), 4.10-4.40 (1H, m), 4.77-4.92 (1H, 8.3Hz), 8.74-8.90 (1H, br), 9.05-9.15 (1H, br) NMR (DMSO-d6, 6): 1.20-1.87 (12H, m), 2.14-2.42 piperidylcarbonyl]-3(S)-ethymyl- β -alanine methyl m), 8.51 and 8:61 (total 1H, d, J=8.0 and IR (Film) : 3300, 2950, 1725, 1640, 1620 $m cm^{-1}$ Mass (m/z): 378 (M^++1) free of compound (2) N-[(R)-1-{3-(4-piperidyl)propionyl}-3ester hydrochloride

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Example 20

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vacuo. The residue was purified by HPLC on C18 silica gel object compound were combined and evaporated in vacuo, and To a solution of N-[(R)-1-{3-(1-benzylexycarbonyl-4-The fractions containing freeze-dried to give N-[(R)-1-{3-(1-benzyloxycarbonyl-4piperidyl)propionyl}-3-piperidylcarbonyl]-2(S) amino-6piperidyl)prop.onyl}-3-piperidylcarbonyl]-2(S)-amino-βtetrahydrofuran (2 ml), ethanol (2 ml) was added a temperature for 1 hour, the mixture was evaporated in solution of lithium hydroxide (17 mg) in water (2 ml) eluting with a solution of 40% CH1CN in 0.1% aqueous. under stirring at 0°C. After stirring at ambient alanine ethyl ester hydrochloride (250 mg.) in trifluoroacetic acid solution.

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NMR (DMSO-d6, 6): 0.87-1.14 (2H, m), 1.24-1.56 (4H, m), 1.60-1.91 (4H, m), 2.09-2.17 (3H, m), 2.59-3.23 (5H, m), 3.32-3.84 (2H, m), 3.93-4.04 (4H, (1H, br), 7.27-7.40 (5H, m), 8.14-8.28 (3H, m) m), 4.13-4.43 (1H, m), 5.06 (2H, s), 4.88-5.28 Mass (m/z): 489 (M^++1) free of compound IR (Nujol): 1770, 1730, 1650 cm⁻¹ alanine trifluoroacetate (230 mg).

Example 21

alanine (1.12 g) in ethyl acetate (12 ml) was added 4N HCl piperidylcarbonyl]-3(S)-ethynyl- β -alanine trifluoroacetate The residue was purified by HPLC on [[α] $_{D}^{20}$ -31.63° (C=1.0, MeOH) : object compound (1)] (0.32 C18 silica gel column eluting with (0.1% trifluoroacetic (1) A solution of $N-[(R)-1-\{3-(1-text-butoxycarbonyl-4$ $piperidyl)propionyl}-3-piperidylcarbonyl]-3-ethymyl-\beta$ acid aqueous solution (TFA): CH3CN = 89:11) to give one -1.47° (C=1.0, MeOH) : in ethyl acetate (6.04 ml) under stirring at 0°C. stirring at ambient temperature for 2 hours, and .somer of N-[(R)-1-{3-(4-piperidyl)propionyl}-3g) and the other isomer $\{\lceil lpha
ceil_D^{20}$ object compound (2)] (0.35.g.) evaporated in vacuo.

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object compc...d ('')

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3.68-3.83 (2H, m), 4.10-4.34 (1H, m), 4.75-4.89 J=8.8Hz), 2.69-2:93 (3H; m), 2.97-3.28 (4H, m), (1H, m), 8.14-8.30 (1H, br), 8.39-8.46 (1H, m), NWR (DMSO-d6, 6): 1.15-1.73 (8H, m), 1.81 (3H, d, J=13.6Hz), 2.08-2:37 (3H, m), 2.5% (2H, d, IR (Film) : 3270, 2930, 1720, 1630 cm-1 8.50-8.61 (1H, br)

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Mass (m/z): 364 (M^++1) free of compound

object compound (2)

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IR (Film) : 3230, 2930, 1725, 1620 cm-1
NWR (DMSO-d₆, 6) : 1.14-1.66 (8H, m), 1.81 (3H, d, J=13.8Hz), 2.08-2.43 (3H, m), 2.58 (2H, d, J=7.6Hz), 2.69-3.00 (5H, m), 3.10-3.29 (4H, m), 3.69-3.85 (1H, m), 4.04-4.16 and 4.31-4.42 (total 1H, m), 8.11-8.27 (1H, br), 8.40-8.45 (1H, m), 8.44-8.59 (1H, br)

 The following compounds were obtained according to a similar manner to that of $\overline{\text{Example 21 (1)}}$.

20 (2) (3R)-N-[(R)-1-{3-(4-Piperidyl)propionyl}-3piperidylcarbonyl]-3-methyl-β-alanine hydrochloride mp: 105-108°C IR (Nujol): 1720, 1620, 1605 cm⁻¹ NMR (DMSO-d₆, δ): 1.04-1.09 (3f, μ, 1.28-1.83 (12H, π), 2.06-2.49 (5H, μ), 2.58-3.23 (6H, π), 3.70-3.83 (1H, π), 4.16-4.33 (1H, π), 7.94 (1H, dd, J=17 and Z, 8Hz), 8.71-8.98 (1H, π), 9.61-9.20 (1H, π) Mass (π/z): 354 (M⁺+1) free of compound

(3) N-[(R)-1-{3-(4-piperidyl)propionyl}-3piperidylcarbonyl]-β-alanine hydrochloride

[\alpha]\frac{2}{6} - 24.3° (C=1.0, MeOH)

mp: 84°C

IR (Nujol): 3320, 1700, 1650 cm⁻¹

NMR (DMSO-d₆, \beta): 1.21-1.65 (7H, m), 1.80 (3H, d, J=13.2Hz), 2.29-2.41 (4H, m), 2.56-3.07 (4H, m), 3.15-3.26 (4H, m), 3.70-3.85 (1H, m), 4.13-4.37 (4H, m), 7.97-8.10 (1H, m), 8.60-8.76 (1H, br), 8.91-9.03 (1H, br)

Mass (m/z): 340 (m⁺+1) free of compound

Elemental Analysis C₁₇H₂₉N₃O₄·HCl-1.5AcOEt-3H₂O (%)

Calcd.: C 49.15, H 8.61, N 7.48

Found: C 49.08, H 8.23, N 7.29

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(4) N-[(R)-1-{3-(4-piperidyl)propionyl}-3piperidylcarbonyl]-3(S)-(4-methoxyphenethyl-aminocarbonyl)-β-alanine hydrochloride
[α]β⁰ = -19.07°C (C=1.0, MeOH)
mp : 82°C

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IR (Nujol): 3280, 1725, 1630, 1600 cm⁻¹

NMR (DMSO-d₆, δ): 0.99-1.69 (10H, m), 2.11-2.82

(11H, m), 2.94-3.09 (4H, m), 3.49 (3H, s), 3.86-4.30 (4H, m), 6;63 (2H, d, J=8.4Hz), 6.90 (2H, d, J=8.5Hz), 7.81-8.19 (2H, m), 8.41-8.68 (1H, br))

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Mass (m/z) : 515 (M⁺-1) free of compound
(5) N-[(R)-1-{3-(4-piperidyl)propionyl}-3piperidylcarbonyl]-3(R)-phenethyl-6-alanine
hydrochloride

53

NMAR (DMSO-d₆, 6): 1.03-1.91 (13H, m), 2.06-3.07 (11H, m), 3.12-3.24 (2H, m), 3.70-3.90 (1H, m), 3.98-4.38 (2H, m), 7.16-7.51 (5H, m), 7.93-8.05 (1H, m), 8.71-9.01 (12H, m), 9.08-9.20 (1H, br)

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IR (Nujol) : 3300, 1700, 1620 cm-1

 $[\alpha]_{6}^{5} = -32.35^{\circ} (C=1.0, MeOH)$

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Elemental Analysis $C_{17}H_{29}N_{3}O_{4} \cdot HCl \cdot 1 \cdot .25AcOEt \cdot 1 \cdot .6H_{2}O(\$)$

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Calcd. : C 51.32, H 8.46, N 8.16

C 51.22, H 8.77, N 7.92

Found

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Calcd. : C 56.80, H 8.27, N 7.95 C 56.94, H 8.01, N 7.58 Mass (m/z): 444 (M++1) free of compound Elemental Analysis C25H37N3O4·HCl·2.7H2O Found

NMR (DMSO-d6, 6): 1.22-1.86 (12H, m), 2.11-3.24 piperidylcarbonyl]-3(R)-(4-methoxyphenethyl)- β -(6) N-[(R)-1-{3-(4-piperidyl)propionyl}-3-IR (Nujol) : 1715, 1620, 1600 cm⁻¹ $[\alpha]_{6}^{20} = 43.1^{\circ} (C=1.0, MeOH)$ alanine hydrochloride

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(12H, m), 3.71-4.36 (5H, m), 3.71 (3H, s), 6.82 (1H, t, J=8.8Hz), 8.63-8.74 (1H, br), 8.90-9.01 (2H, d, J=8.6Hz), 7.08 (2H, d, J=8.5Hz), 7.90 (1H, br)

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C 57.19, H 8.12, N 7.69 Found : C 56.82, H 8.17, N 7.51 Mass (m/z): 474 (M^++1) free of compound Elemental Analysis C26H39N3O5·HCl·2H2O Calcd. :

piperidylcarbonyl]-2-(2-piperidyl)acetic acid (7) N-[(R)-1-{3-(4-piperidyl)propionyl}-3hydrochloride

4.87-5.02 (1H, m), 8.65-8.84 (1H, br), 8.96-9.10 (2H, m), 2.56-3.23 (6H, m), 3.70-4.55 (8H, m), NMR (DMSO-dg, 5): 1.27-1.83 (16H, m), 2.23-2.40 IR (Nujo1) : 3350, 1705, 1600 cm-1 (1H, br)

Mass (m/z): 394 (M^++1) free of compound

NMR (DMSO-d6, 6) : 1.29-1.50 (5H, m), 1.77-1.83 (2H, m), 2.30-2.60 (4H, m), 2.70-2.94 (2+1/2H, m), morpholinylcarbonyl]-8-alanine hydrochloride IR (Nujol): 3300, 1705, 1625 cm-1 (8) N-[4-{3-(4-piperidyl)propionyl}-2-

4.05 (3+1/2H, m), 4.43-4.49 (1/2H, m), 7.79-7.97 3.08-3.35 (5+1/2H, m); 3.40-3.57 (1H, m), 3.72-(1H, m), 8.73-8.89 (1H, br), 9.04-9.16 (1H, br) Mass (m/z): 342 (M^++1) free of compound

pipėridylcarbonyl]-3-phenyl-β-alanine hydrochloride (9) N-[(R)-1-{3-(4-piperidyl)propionyl}-3-IR (Nujol): 1710, 1630, 1600 cm-1 2°19 : dw

8.49-8.66 (lH, m), 8.80-8.94 (lH, br), 9.06-9.20 3.63-3.86 (1H, m), 4.08-4.41 (1H, m), 5.18 (1H, (3H, m), 2.59-3.09 (5H, m), 3.14-3.25 (2H, m), q, J=7.8Hz), 7.20-7.27 (1H, m), 7.31 (5H, s), NWR (DMSO-d6, 6): 1.24-1.91 (10H, m), 2.10-2.41 (1H, br)

Mass (m/z) : 416 (M^++1) free of compound

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NMR (DMSO-d6, 6) : 1:01-1.50 :9H, m), 1.66-1.83 (8H, piperidylcarbonyl]-3(R)-(3,4-dimethoxyphenethyl)- β -(10) N-[(R)-1-{3-(4-piperidyl)propionyl}-3- $[\alpha]_{b}^{0} = -13.33^{\circ}$ (C=1.0, MeOH) IR (Nujol): 1730, 1635 cm-1 alanine hydrochloride

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6.85 (2H, m), 8.88-9 f2 (1H; bx), 9.15-9.25 (1H, 6), 4.15-4.38 (2H, m), 6.15-6.69 (1H, m), 5.77- $(-\infty)$, $(\pm .83 - 3 \cdot 23 \cdot (113, -m))$, 3 $(113 \cdot (314, s))$, $(3.73 \pm (314, s))$

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Mass (m/z): 504 (M^++1) free of compound

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(9H, m), 3.17-3.29 (2H, m), 3.73 (3H, s), 3.97-NMR (DMSO-d6, 6): 1.13-2.00 (14H, m), 2.01-3.70 piperidylcarbonyl}-3(S)-(3-methoxyphenethyl)- β -(11) N-[(R)-1-{3-(4-piperidyl)propionyl}-3-IR (Nujol): 1710, 1600, 720 cm⁻¹ alanine.hydrochloride

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4.08 (1H, m), 4.10-4:37 (1H, m), 6.74 (3H, d
                                    like), 7.18 (1H, t like), 7.92 (1H, t like),
                                                                                                            Mass (m/z): 474 (M^++1) free of compound
                                                                        8.72 (lH, br), 8.99 (lH, br)
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piperidylcarbonyl]-2(S)-benzoylamino-\beta-alanine (12) N-[(R)-1-{3-(4-piperidyl)propionyl}-3hydrochloride

NMR (DMSO-d6, 6): 1.2-1.85 (12H, m), 2.27-2.36 (2H, m), 2.57-3.10 (4H, m), 3.12-3.25 (2H, m), 3.39-3.82 (3H, m), 4.07-4.59 (3H, m), 7.45-7.56 (3h, m), 7.87-7.91 (2H, m), 8.22-8.40 (1H, m), 8.65-Mass (m/z): 459 (M^++1) free of compound 8.75 (1H, m), 8.89-9.02 (1H, m) IR (Nujol): 3100, 1725, 1630 cm⁻¹

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piperidylcarbonyl]-3(R)-(3-trifluoromethylphenethyl)-IR (Nujol) : 3300, 1715, 1630, 1610 cm-1 (13) $N-[(R)-1-\{3-(4-piperidyl)propionyl\}-3 [\alpha]_{b}^{0} = -21.4^{\circ} (C-1.0, MeOH)$ β-alanine hydrochloride mp: 118°C

20

MMR (DMSO-d_{6/2}6) : 142352323(14H, m), 2.35-2.45

25 / 京和高島高級東京 3 8 3 2 2 3 3 3 3 3 3 3 3 4 10 (1H, m), 4 15 4 4 1 マンシン 文化を資金を示(1H, m), 7.49-7.55 (4H, m), 7.94-8.05 (1H, m), ..get 5(5H com), 0.2 461-2, 83 (5H, m), 3.15-3.28 (2H, m), Mass (m/z): 512 (M^++1) free of compound Elemental Analysis $\mathsf{C}_2\mathsf{e}^{\mathrm{H}_3}\mathsf{e}^{\mathrm{F}_3}\mathsf{N}_3\mathsf{O}_4$ ·HCl · 1.8 $\mathsf{H}_2\mathsf{O}$ 8.75-8.93 (1H, m), 9.03-9.17 (1H, m) 見のます

C 53.80, H 7.05, N 7.24 C 53.72, H 7.10, N 7.02

Çalcd.

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Found

Pitridylcarbonyl]-2(S)-phenylsulfonylamino-\$-alanine (14) N-[(R)-1-{3-(4-piperidy1)propiony1}-3hydrochloride

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4.12-4.39"(2H, m), 7.55-7.62 (3H, m), 7.75-7.79 (2H, m), 8.01-8.26 (2H, m), 8.50-8.66 (1H, br), (3H, m), 2.70-3.40 (7H, m), 3.74-3.91 (2H, m), NMR (DMSO-d6, 6) : .1.21-1.83 (11H, m), 2.04-2.37 Mass (m/z): 495 (M^++1) free of compound $[\alpha]\beta^5 = -14.23^{\circ} (C=1.0, MeOH)$ IR (Nujol) : 1720, 1630 cm⁻¹ 8.82-8.94 (1H, br)

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(11H, m), 3.75 (3H, s), 3.70-3.89 (1H, m), 4.12m), 7.84-7.94 (1H, m), 8.60-8.75 (1H, bz), 8.91-4.39 (1H, m), 6.81-6.94 (2H, m), 7.07-7.20 (2H, NMR (DMSO-d6, 6): 1.21-1.91 (16H, m), 2.30-3.24 $\texttt{piperidylcarbonyl]-3(R)-(2-methoxyphenethyl)-}\beta-$ Mass (m/z): 474 (M^++1) free of compound (15) N-[(R)-1-{3-(4-piperidyl)propionyl}-3-IR (Nujol) : 1725, 1640, 1600 cm-1 $[\alpha]_{60}^{0} = -17.73^{\circ} (C=1.0, MeOH)$ alanine hydrochloride 9.03 (1H, br) 10 20

 $\label{localidylcarbonyl} Piperidylcarbonyl] - 2(S) - (n-butanesulfonylamino) - \beta -$ (16) N-[(R)-1-{3-(4-piperidyl)propionyl}=3alanine hydrochloride

NMR (DMSO-d6, 8): 0.88 (3H, t, J=7.2Hz), 1.14-1.89 (15Н, й), 2.29-2.40 (2К, м), 2.77-3.06 (6Н, м), 3.19-3.27 (2H, m), 3.77-4.41 (5K, a), 7.51-7.60 (1H, m), 8.04-8.18 (1H, m), 8.43-8.38 (1H, m), 8.43-8.60 (1H, br), 8.73-8.86 (1H, br) Mass (m/z): 475 (M^++1) free of compound $(\alpha)_{D}^{5} = -31.37^{\circ} (C=1.0, MeOH)$ IR (Nujol): 1715, 1620 cm-1 25 30

Piperidylcarbonyl]-3(R)-(3,4,methylenedioxy-(17) N-[(R)-1-{3-(3-piperidyi)propionyl; .3-

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phenethyl)-\$-alanine hydrochloride $[\alpha]_{6}^{5}: -17.27^{\circ} (C=1.0, MeOH)$

m), 1.06-3.28 (12H, m), 3.60-4.27 (5H, m), 4.30-NMR (DMSO-d6, 6): 0.84-1.50 (6H, m); 1.59-1.91 (6H, 4.40 (1H, m), 5.95 (2H, s), 6.59-6.63 (1H, m), 6.75-6.81 (2H, m), 7.84-7.90 (1H, m) IR (Nujol) : 1725, 1685, 1620 cm-1

C 56.77, H 7.55, N 7.36 C 56.81, H 7.69, N 7.11 Elemental Analysis C26H37N3O6·HCl·1/4EtOAc·1.4H2O Mass (m/z): 488 (M^++1) free of compound Calcd. : Found

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NMR (DMSO-d₆, 5) : 1.27-1.83 (11H, m), 2.08-2.32 IR (KBr) : 3425, 3250, 1726, 1638, 1614 cm⁻¹ piperidylcarbonyl]-3(S)-ethynyl-\$-alanine (18) N-[(R)-1-{3-(4-piperidyl)propionyl}-3hydrochloride

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3.75-3.80 (1H, m), 4.08-4.32 (1H, m), 4.79-4.82 (1H, m), 8.42-8.54 (1H, m), 8.75 (1H, br), 9.04 (3H, m), 2.58-3.09 (5H, m), 3.18-3.22 (3H, m), (1H, br)

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Mass (m/z) : 364 (M*+1) free of compound

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... NMR (DMSO-d6, 6): 1.25-1.52 (7H, m), 1.69-1.86 (4H, m), 2.21-2.46 (6H, m), 2.69-3.06 (4H, m), 3.15-3.26 (2H, m), 3.47-3.84 (2H, m), 4.14-4.24 (1H, m), 7.80-7.97 (1H; m), 8.64-8.78 (1H, br) 8.95-... piperidyl succinamic acid hydrochloride 196 78 (Rujol) : 3200, 1710, 1620 cm-1 (19) N-[1-(3-(4-piperidy1)propiony1}-3-.9.06 (1H, br)

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Mass (m/π) : 340 (M^++1) tree of compound

(20) N-[(R)-1-{3-(4-piperidy1)propiony1}-3-

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piperidylcarbonyl]-3(S)-propargylaminocarbonyl-ß- $[\alpha]_{6}^{0} = -11.9^{\circ} (C=1.0, MeOH)$ alanine hydrochloride

IR (Nujol) : 1735, 1640 cm^{-1}

NMR (DMSO-d6, "6) : 1.21-1.69 (7H, m), 1.75-1.86 (3H, m), 2.06-2.40 (3H, m), 2.56-3.04 (5H, m), 3.17-3.26 (4H, m), 3.68-3.87 (3H, m), 4.08-4.56 (3H, m), 8.11-8.30 (1H, m), 8.34-8.50 (1H, m), 8.60-8.73 (1H, br), 8.90-9.02 (1H, m)

Mass (m/z): 421 (M^++1) free of compound

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(21) 4-[3-{3-(4-piperidy1)propionylamino}-1-piperidyl]-4oxo-butyric acid hydrochloride

IR (Nujol) : 1735, 1700, 1610 cm-1

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NMR (DMSO-d6, 6) : 1.25-1.50 (9H, m), 1.71-1.83 (4H, m), 2.06-2.16 (2H, m), 2.39-2.46 (3H, m), 2.70-2.87 (2H, m), 2.96-3.08 (1H, m), 3.15-3.25 (2H, m), 3.52-3.76 (2H, m), 4.08-4.16 (1H, m), 7.84, 7.95 (total 1H, d, J=7.8 and 6.5Hz), 8.73-8.88 (1H, br), 9.00-9.10 (1H, br)

Mass (m/z): 340 (M^++1) free of compound

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IR (Film) : 3250, 2930, 2850, 1760, 1700, 1610 cm-1 carbonyl]-3(R)-ethynyl- β -alanine trifluoroacetate (22) N-[(S)-1-{3-(4-piperidyl)propionyl}-3-piperidyl- $[\alpha]^{6}_{6} = 35.7^{\circ} \text{ (C=0.65, MeOH)}$

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MAR (DMSO-d6, 8): 1.14-1.84 (1H, m), 2.09-2.40 (3H, .* m), 2.57-3.28 (9H. m), 3.69-3.83 (1H, m), 4.08-

4.33 (1H, m), 4.75-4.86 (1H, m), 4.14-8.29 (1H, hr), 8.38-8.47 (1H, m), 8.49-6 (0 (1H, br) Mass (m/z): 364 (M^++1) free of compound

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IR (Film) : 3250, 2930, 2850, 1740, 1700, 1610 cm⁻¹ carbonyl]-3(S)-ethynyl- β -alaninetrifluoru acetate N-[(S)-1-{3-(4-piperidyl)propionyl}-3-piper/ayl-

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MMR (DMSO-d₆, 6): 1.15-1.85 (11H, m), 2.05-2.40 (3H, m), 2.56-3.00 (6H, m), 3.11-3.28 (3H, m), 3.70-3.88 (1H, m), 4.05-4.15 and 4.30-4.44 (total 1H, m), 4.75-4.90 (1H, m), 8.15-8.30 (1H, br), 8.40-8.49 (1H, m), 8.49-8.60 (1H, br) Mass (m/z): 364 (M⁺+1) free of compound

Example 22

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A mixture of N-[1-{2-(1-benzyloxycarbonyl-4-piperidyloxy)acetyl}-3-piperidylcarbonyl]- β -alanine (1.16 g) and 10% Pd-C (0.23 g, 50% wet) in a solution of 1N HCl (2.44 ml) and tetrahydrofuran (20 ml) was hydrogenated at atmospheric pressure for 2 hours. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo and freeze-dried to give N-[1-{2-(4-piperidyloxy)acetyl}-3-piperidylcarbonyl]- β -alanine hydrochloride (0.69 g).

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IR (Nujol) : 3290, 1700, 1625 cm⁻¹

NMR (DMSO-d₆, 6): 1.15-2.09 (9H, m), 2.11-2.69 (2H, m), 2.84-3:25 (8H, m), 3.56-3.74 (2H, m), 4.07-4.32 (3H, m), 8.06-8.24 (1H, m)

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Mass (m/z): 342 (m^++1) free of compound Elemental Analysis $C_16H_27N_3O_5$ ·HCl·1.8H2O (\$)

. 52

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(1) A mixture of N=[(R)-1-(3-(1-benzyloxycarbonyl-4-piperidyl)propionyl)-3-piperidylcarbonyl]-2(S)-acetylamino-b-alanine (67 mg) and 10% Pd-C (15 mg, 50% wet) in a mixture of 1N HCl (0.13 ml) and tetrahydrofuran (2 ml) was hydrogenated at atmospheric pressure for 1 hour. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was dissolved in water (5 ml) and then freeze-dried to give

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N-[(R)-1-{3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-2(S)-acetylamino- β -alanine hydrochloride (50 mg). [α] δ^5 = -21.37° (C=0.75, MeOH) IR (Nujol) : 1720, 1640, 1610 cm⁻¹ NMR (DMSO-d6, δ) : 1.20-1.82 (12H, m), 1.85 (3H, s), 2.10-2.43 (5H, m), 2.59-3.27 (4H, m), 3.74-3.83 (2H, m), 4.14-4.37 (2H, m), 8.02-8.19 (2H, m), 8.42-8.59 (1H, br), 8.72-8.84 (1H, br) Mass (m/z) : 397 (m+1) free of compound

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The following compounds were obtained according to a similar manner to that of Example 23 (11).

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- (2) N-[2-[1-{3-(4-piperidy1)propiony1}-3piperidy1]acety1]glycine hydrochloride IR (Film): 3350, 2940, 1715, 1630 cm⁻¹ NMR (DMSO-d6, 6): 1.11-1.82 (12H, m), 2.00-2.11 (2H, m), 2.24-2.40 (2H, m), 2.62-3.03 (4H, m), 3.20 (2H, d, J=12.6Hz), 3.64-3.82 (3H, m), 4.24 (1H, m), 8.25-8.35 (1H, m), 8.75-8.91 (1H, br), 9.09-9.20 (1H, br) Mass (m/z): 340 (M⁺=1) free of compound
- (3) N-[1-{3-(4-piperidyl)propion_1}}-3-r__ceridylcarbonyl]3-methyl-\$\beta\$-alanine hydrochloride

 IR (Nujol): 3250, 1705, 1610 cm^1

 NMR (DMSO-d6, 6): 1.04-1.09 (3H, m), 1.28-1.83

 (11H, m), 2.10-3.44 (9H, m), 3.7L^3.83 (1H, m),
 3.98-4.34 (2H, m), 7.86-7.96 (1H, m), 8.74-8.87

 (1H, m), 9.01-5.1. (1H, m)

 Mass (m/z): 354 (M+1) free of compound

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(4) N-[(R)-1-{2-(4-piperidyloxy)acetyl}-3-piperidylcarbonyl'-6-alanine ethyl ester hydrochloride
IR (Film, : 2930, 1720, 1625 cm⁻¹

NMR (DMSO-d₆, 8) : 1.18 (3H, t, J=7.1Hz), 1.46-2.47 3.55-3.72 (2H, m), 4.05 (2H, g, J=7.1Hz), 4.17-(11H, m), 2.60-2.70 (1H, m), 2.86-3.27 (8H, m), 4.30 (2H, m), 8.06-8.21 (1H, m), 9.00-9.14 (2H,

Mass (m/z): 370 (M^++1) free of compound

(5) N-[1-{3-(4-piperidyl)propionyl}-1,2,3,4-tetrahydro-3-NMR (DMSO-d₆, 6) : 1.12-1.89 (9H, m), 2.10-2.21 (2H, 4.26 (2H, t, J=7.0Hz), 7.06-7.20 (4H, m), 8.13m), 2.39 (2H, d, J=6.7Hz), 2.70-3.84 (7H, m), quinolylcarbonyl]-\balanine hydrochloride IR (Film) : 3450, 3930, 1720, 1630 cm-1 8.24 (1H, m)

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Mass (m/z): 386 $(M^{+}-1)$ free of compound

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NMR (DMSO-d₆, 6) : 1.24-2.07 (9H, m), 2.11-2.69 (2H, m), 2.89-3.27 (8H, m), 3.57-3.74 (2H, m), 4.07piperidylcarbonyl]-\balanine hydrochloride Mass (m/z): 342 (M^++1) free of compound IR (Film): 3290, 2920, 1710, 1620 cm⁻¹ (6) N-[(S)-1-{2-(4-piperidyloxy)acetyl}-3-4.30 (3H, m), 8.03-8.87 (1H, m)

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piperidylcarbonyl]-2(S); (n.hexanoylamino)-β-alanine (7) N-[(R)-1-{3-(4-pigeridyl)propionyl}-3-1. 14 19 19 19 19 19 19 19 $[\alpha]_{0}^{20} = -27.7^{\circ}$ (C=1.0, MeOH) (7 hydrochloride 23

mp : .156-157°C

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(17H, m), 2.10 (2H, t, J=7.4Hz), 2.27-3.82 (12H .: NMR (DMSO-d6, 6): 0.85 (3H, t, J=6.5Hz), 1.55-1.88 m), 4.14-4.35 (2H, m), 7.97-8.10 (2H, m), 8.37-IR (Nujol): 3200, 1720, 1560, 1600 cm-1 (m/z) : 453 (x+1) free of compound 8.51 (1H, br), 8.69-8.89 (1H, br)

Mass

. 32

piperidylcarbonyl]-2(S)-(4-chlorobenzoylamino)- β -N-[(R)-1-{3-(4-piperidyl)propionyl}-3alanine hydrochloride

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IR (Nujol) : 3200, 1730, 1710, 1640 cm-1 $[\alpha]_{1}^{0} = -35.6^{\circ} (C=1.0, MeOH)$

4.18-4.35 (1H, m), 4.44-4.54 (1H, m), 7.44-7.59 (3H, m), 2.60-3.25 (6H, m), 3.34-3.82 (3H, m), (2H, m), 7.84-7.92 (2H, m), 8.18-8.31 (1H, m), NMR (DMSO-d6, 6): 1.16-1.85 (11H, m), 2.11-2.34

Mass (m/z): 493 (M^++1) free of compound 8.41-8.55 (1Н, т), 8.60-8.83 (2Н, т)

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<code>piperidylcarbonyl]-2(S)-(4-methoxybenzoylamino)-eta-</code> (9) N-[(R)-1-{3-(4-piperidyl)propionyl}-3alanine hydrochloride

IR (Nujol): 3210, 1720, 1620, 1600 cm⁻¹ $[\alpha]_{B}^{0} = -31.8^{\circ} (C=1.0, MeOH)$

(3H, m), 2.60-3.79 (8H, m), 3.82 (3H, s), 4.10-J=8.8Hz), 7.55 (2H, d, J=8.1Hz), 8.13-8.31 (1H, 4.35 (1H, m), 4.44-4.54 (1H, m), 7.02 (2H, d, NMR (DMSO-d6, 8): 1.11-1.89 (12H, m), 2.12-2.39 m), 8.44-8.55 (2H, m), 8.70-8.84 (1H, m)

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Mass. (m/z) : .489 (M+3) free of compound

piperidylcarbonyl]-2(S)-amino-eta-a.anine hydrochloride (4H, 'a), 2.58-3.24 (2H, m), 3.50-3.57 (2H, m), NMR (DMSO-d6, 6) : 1.19-1.91:(12H, m), 2.07-2.43 3.74-4.40 (3H, m), 8.30-8.96 (5H, m) IR (Film) : 3250, 2910, 1745, 1640 cm-1 (10): N-[(R)-1-{3-(4-pipericyl)propiony!)-3-

Mass (m/z): 355 (M^++1) free of compound

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(cyclohexyloxycarbonyloxy)ethyl ester hydrochloride piperidylcarbonyl]-2(S)-benzoylamino-\beta-alanine 1-(11) N-[(R)-1-{3-(4-piperidy1)propiony1}-3-

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IR (Nujol): 3240, 1750, 1640 cm-1

J=5.7Hz), 2.11-2.39 (3H, m), 2.58-3.25 (2H, m), 3.35-4.40 (7H, m), 4.49-4.66 (2H, m), 6.63 (1H, NMR (DMSO-d6, 8) : 1.01-1.91 (23H, m), 1.76 (3H, d, t, J=5.1Hz), 7.43-7.57 (5H, m), 7.85-7.95 (1H,

Mass (m/z) : 629 (M^++1) free of compound

NMR (DMSO-d6, 6) : 1.16-1.54 (6H, m), 1.64-1.85 (6H, m), 2.24-2.34 (1H, m), 2.63-3.03 (5H, m), 3.13-3.84 (7H, m), 4.70-4.83 (1H, m), 7.41-7.53 (3H, (12) N-{1-{3-(4-piperidyl)propionyl}-3-piperidyl]-2(S)m), 7.83-7.90 (2H, m), 8.60-8.72 (1H, m) benzoylaminosuccinamic acid hydrochloride Mass (m/z): 459 (M^++1) free of compound IR (Nujol) : 3300, 1720, 1630 cm-1

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3 74-3.83 (2H, m), 4.15-4.35 (2H, m), 8.64-8.22 (12H, m), 2.10-2.43 (3H, m), 2.60-3.34 (7H, m), NMF (DMSO-d6, 6): 0.67 (4H, d, J=5.3Hz), 1.18-1.84 (1H, m), 8.39 (1H, dd, J=19.6 and 7:9Hz) / 8:51- $\texttt{piperidylcarbonyl} \] - 2(S) - \texttt{cyclopropylcarbonylamino-} \beta -$ 8.69 (1H, cbr), 8.82-8.86 (1H, br) South to Mass (m/z) : . 423 (M+1) free of compound (13) N-[(R)-1-{3-(4-piperidyl)propionyl}-3-IR (Nujol): 1715, 1645, 1610 cm-1 $[\alpha]_{60}^{0} = -20.2^{\circ} (C=1.0, MeOH)$ alanine hydrochloride

22

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 $\texttt{piperidylcarbonyl} \ \texttt{J-2(S)-(3-methoxypropionyl)} \\ \texttt{amino-} \\ \texttt{\beta-}$ NMR (DMSO-d6, 5): 1.12-1.89 (15H, m), 2.11-2.43 IR (Nujol): 3250, 1720, 1650, 1610 cm⁻¹ (14) N-[(R)-7-{3-(4-piperidyl)propionyl}-3- $[\alpha]^{0}_{0} = -20.2^{\circ}$ (C=1.0, MeOH). alanine hydrochloride 30

32

m), 3.21 (3H, s), 3.25-3.44 (2H, m), 3.52-2H, t, J=6.5Hz), 3.61-3.84 (2H, m), 4.14-4.39 (2H, m), (3H, m), 2.37 (2H, t; J=6.5Hz), 2.72-3.12 (3H, 7.94-8.09 (2H, m)

Mass (m/z): 441 (M^++1) free of compound

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 $\texttt{piperidylcarbonylj-2(R)-benzoylamino-} \beta-\texttt{alanine}$ (15) N-[(R)-1-{3-(4-piperidyl)propionyl}-3- $[\alpha]_{\beta}^{0} = -14.3^{\circ} (C=1.0, MeOH)$ hydrochloride

IR (Nujol): 1750, 1730, 1640 cm-1

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4.12-4.61 (2H, m), 7.45-7.63 (3H, m), 7.88-7.97 (6H, m), 3.10-3.26 (2H, m), 3.37-3.84 (3H, m), (2H, m), 8.28-8.45 (1H, m), 8.72-8.77 (1H, m), NMR (DMSO-d6, 8): 1.15-1.86 (12H, m), 2.25-3.05 8.66-8.84 (1H, br), 8.97-9.11 (1H, br) Mass (m/z): 459 (M^++1) free of compound

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3.36-3.34 (4h, m), 4.01-4.51 (2H, m), 6.83 (2h, (2H, m), 8.56-8.71 (1H, br), 8.85-8.98 (1H, br) (3-, m) 2.60-3.06 (3H, m), 3.11-3.23 (2H, m), d, J=8.5Hz), 7.76 (2H, d, J=8.6Hz), 8.20-8.46 $\label{eq:piperidylcarbonyl]-2(S)-(4-hydroxybenzoylamino)-\beta-} piperidylcarbonyl]-2(S)-(4-hydroxybenzoylamino)-\beta-$ NF. (DMSG 66, 6): 1.17-1.85 (12H, m), 2.11-2.38 IR (Nujol): 1715, 1630, 1640, 1600 cm-1 Mass (m/z): 473 (M^+-1) free of compound (16) N-[(R)-1-{3-(4-piperidyl)propionyl}-3- $[\alpha]$ $\beta^0 = -40.5 (C=1.0, MeOH)$ alanine hydrochloride

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IR (KBr, pellet) : 2949, 2393, 1734, 1718, 1651 cm⁻¹ (1H, m), 2.61-3.07 (4H, m), 3.13-3.85 (8H, m), (17) N-[1-{3-(4-piperidyl)propionyl}-3-piperidyl]-3(S)-NMR (DMSO-d₆, 6): 1.16-1.89 (11H, m), 2.11-2.38 benzoylaminosuccinamic acid hydrochloride

4.66-4.86 (1H, m), 7:44-7.59 (3H, m), 7.85-7.88 (2H, m), 7.93-8.11 (1H, m), 8.44-8.60 (1H, br), 8.63-8.74 (1H, m), 8.77-8.90 (1H, br) Mass (m/z): 457 $(M^{+}-1)$ free of compound

(18) N-[1-{3-(4-piperidyl)propionyl}-3-piperidyl]-2(S)-IR (KBr, pellet) : 3057, 2945, 2864, 1734, 1653, acetylaminosuccinamic acid hydrochloride 1618 cm-1

NMR (DMSO-d₆, 6) : 1.20-1.59 (7H, m), 1.73-1.97 (4H, 4.43-4.59 (lh, m), 7.81-8.21 (2H, m), 8.56-8.76 m), 1.83 (3H, s), 2.24-2.36 (2H, m), 2.44=3.10 (4H, m), 3.17-3.28 (3H, m), 3.47-4.21 (4H, m), (1H, br), 8.89-9.03 (1H, br)

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Mass (m/z): 397 (M^++1) free of compound

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piperidylcarbony]]-2(R)-acetylamino- β -alanine (19) N-[(R)-1-{3-(4-piperidyl)propionyl}-3- $[\alpha]_{60}^{20} = -21.7^{\circ} \text{ (C=1.0, MeOH)}$ hydrochloride

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8.00-8.20 (2H, m), 8.30-8.46 (1H, br), 8.61-8.74 (2.09-2.65 (4H, m), 2.70-3.08 (2H, m), 3.15-3.34 IR (KBr, pellet) : 2947, 2864, 1734, 1653, 1616 $m cm^{-1}$ NMR (DMSO-dg., 6) : 1.17-1.90 (12H, m), 1.85 (3H, s), (3H, m), 3.60-3.88 (2H, m), 4.17-4.40 (2H, m), (1H, br) 化二次分类的

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Mass (m/z): 397 (M^++1) free of compound

(5H, m), 7.85-7.88 (2H, m), 8.42m8.60 (1H, br), 8.75-IR (KBr, pellet) : 2947, 2864, 1734, 1647, 1605 cm⁻¹ m), 2.18-2.35 (1H, m), 2.60-3.26 (8H, m), 3.45-3.86 (4H, m), 4.69-4.84 (1H, m), 7.45-7.56 (3H, (20) N-[1-{3-(4-piperidyl)propionyl}-3-piperidyl]-3(R)-NMR (DMSO-d6, 8) : 1.15-1.55 (7H, m), 1.64-1.89 benzoylaminosuccinamic acid hydrochloride

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8.89 (1H, br), 8.61-8.75 (1H, m)

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Mass (m/z): 459 (M^++1) free of compound

IR (KBr, pellet) : 2947, 2729, 1734, 1647, 1608 cm⁻¹ 8.57-8.80 (1H, br), 8.68-8.82 (1H, m), 8.92-9.02 4.10-4.60 (4H, m), 7.41-7.54 (3H, m), 7.74-7.82 piperidylcarbonyl]-2(S)-(4-biphenylcarbonylamino)- β -(2H, m), 2.63-3.26 (5H, m), 3.40-3.86 (4H, m), (4H, m), 7.98-8.01 (2H, m), 8.25-8.43 (1H, m), NMR (DMSO-d6, 6) : 1.14-1.86 (10H, m), 2.20-2.36 (21) N-[(R)-1-{3-(4-piperidyl)propionyl}-3alanine hydrochloride (1H, br)

Mass (m/z): 535 (M^++1) free of compound

Example 24

15

was collected by filtration to give $N-\{1-\{3-(4-piperidy1)$ piperidy1)propiony1}-3-piperidy1carbony1]-0-alanine (1.58 at ambient temperature for 2 hours, resulting precipitate acetate (13.5 ml) under stirring at 0°C. After stirring propionyl}-3-piperidy.cerbonyl]-8-alanine:hydrochloride g) in ethyl acetate (16 ml) was added 4N HCl in ethyl (1) A solution of N-[1-{3-(1-tert-butoxycarbonyl-4-

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4.13-4.40 (1H, m), 7.97-8.18 (IH, m), 8.76-8.86 (6H, m), 2.60-3.24 (7H, m), 3.70-3.84 (1H, m), NMR (DMSO-d6, -6) : 1.29-1.83 (10H, m), 2.09-2.42 IR (For) : 3200, 2850, 1780, 1600 cm⁻¹ (1H, m), 9:09-9.23 (1H, m)

mr : 70-72°C

Mass (m/z): .340 (M^++1) free of compound

The following compounds were obtained according to similar manner to that of Example 24 (1)

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(2) N-[1-{3-(4-Piperidyl)propionyl}-4-piperidylcarbonyl]-
                                          B-alanine hydrochloride
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J₀59-E9 : dw

IR (KBr): 3250, 2800, 1710 cm⁻¹

3.79-3.98 (1H, m), 4.30-4.40 (1H, m), 4.30-4.40 (5H, m), 2.48-3.12 (4H, m), 3.10-3.30 (4H, m), (lH, m), 7.98 (lH, t, J=5.4Hz), 8.85-8.98 (lH, NMR (DMSO-d6, 6): 1.28-1.90 (11H, m), 2.23-2.40

Mass (m/z): 340 (M^++1) free of compound br), 9.13-9.21 (1H, br)

2

(3) N-[2-[1-{2-(4-Piperidyl)acetyl}-3-piperidyl]acetyl]β-alanine hydrochloride

mp: 73°C

IR (Nujol): 3200, 1725, 1605 cm-1

13

NMR (DMSO-d6, 6) : 1.22-1.51 (4H, m), 1.68-1.87 (3H, m), 1.92-2.09 (4H, m), 2.23-2.30 (2H, m), 2.35-2.45 (3H, m), 2.60-3.02 (4H, m), 3.16-3.31 (5H, m), 3.67-3.81 (1H, m), 4.11-4.28 (1H, m), 8.00-

8.16 (1Н, ш)

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Mass (m/z): 340 (M^++1) free of compound

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Elemental Analysis C₁₇H₂₉N₃O₄·HCl.1:5AcOEt.2H₂O (%)

(4) N-[1-{4-(4-Piperidyl)butyryl}-3-piperidylcarbonyl]glycine hydrochloride

IR (Nujol): 1740 cm-1

(3H, m), 2.60-3.14 (5H, m), 3.17-3.28 (2H, m), NMR (DMSO-d6, 5): 1.20-1.94 (13H, m), 2.30-2.40 3.72-4.00 (2H, m), 4.00-4.10 and 4.09-4.17

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Mass (m/z): 340 (M^++1) free of compound (total 1H, m), 8.28-8.43 (1H, m)

Elemental Analysis C₁₇H₂₉N₃O₄·HCl·1.25AcOEt·1.5H₂O(%) Calcd.: C 51.51, H 8.45, N.8.19

35

C 51.38, H 8.43, N 8.00 Found:

 $\label{eq:piperidylacetyl} Piperidyl] = \beta - \alpha lanine \ hydrochloride$ (5) N-[2-[1-{2-(4-Piperidylidene)acetyl}-3ე,69 : du

IR (Nujol): 3200, 1730 cm-1

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NMR: (DMSO-d₆, 5) : 1.08-1.41 (3H, m), 1.60-1.76 (3H, m), 1.76-1.92 (3H, m), 1.92-2.04 (2H, m), 2.39

4.04-4.28 (1H, m), 6.04 and 6.08 (total 1H, s), (2H, t, J=6.5Hz), 2.44-2.51 (3H, m), 2.60-2.83 (3H, m), 2.93-3.50 (4H, m), 3.69-3.84 (1H, m), 8.01-8.17 (1H, m)

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Elemental Analysis $C_{17}H_{27}N_{3}O_{4}\cdot HCl\cdot 1.5AcOEt\cdot 2.5H_{2}O$ (%) (m/z): 338 (M^++1) free of compound

Calcd. : C 50.50, H 7.55, N 7.68 C 50.29, H 7.91, N 7.66 Found

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 $piperidylcarbonyl]-3(S)-phenylsulfonylmethyl-\beta-$ (6) N-[(R)-1-{3-(4-piperidyl)propionyl}-3alanine hydrochloride

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IR (Nujol): 1730, 1650, 1610 cm-1

NMR (DMSO-d6, 6) : 1.28-1.83 (13H, m), 2.25-2.34

4.18-4. (1H, n); 7.61-7.76 (3H, m), 7.85-7.99 (2H, m) 8.02-8.13.(1H, m), 8:76 (1H, br), 9.03 (2H, m), 2.48-3.23 (9H, m), 3.54-3.67 (2H, m),

Mass (m/z) :. 492 (M^++1) free of compound

(1H, br)

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Example 25

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ester (0.78 g) in ethyl aretate (8 ml) was added 4N HCl in ${\tt piperidyl)pyropionyl} \verb|--3-piperidylcarbonyl]-$\beta-alanine ethyl$ (1) A solution of N-[(R)-1-(3-(1..text-butoxycarbonyl-4ethyl acetate (4.17 ml) under stirring at 0°C. After stirring at ambient temperature for 2 hours, and

evaporated in vacuo and freeze-dried to give $N-[(R)-1-\{3-1\}]$

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(4-piperidy1)propiony1}-3-piperidylcarbony1}-b-alanine ethyl ester hydrochloride (0.59 g).

IR (Film): 3320, 1700, 1605 cm⁻¹

NMR (DMSO-d₆, 6): 1.18 (3H, t, J=7.1Hz), 1.26-1.65 m), 2.75-3.10 (3H, m), 3.17-3.30 (4H, m), 3.70-(4H, m), 8.01-8.13 (1H, m), 8.63-8.78 (1H, br), 3.84 (1H, m), 4.05 (2H, q, J=7.2Hz), 4.17-4.38 (7H, m), 1.80 (2H, d, J=13Hz), 2.06-2.70 (5H, 8.95-9.06 (1H, br)

Mass (m/z) : 368 $(M^{+}+1)$ free of compound

2

The following compounds were obtained according to a similar manner to that of Example 25 (1)

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(2) (3R)-N-[(R)-1-{3-(4-Piperidyl)propionyl}-3-piperidyl-IR (Nujol) : 3300, 2930, 2850, 1710, 1640, 1610 cm $^{-1}$ (12H, m), 2.29-2.46 (4H, m), 2.58-3.25 (7H, m), J=8.2Hz), 8.52-8.72 (1H, br), 8.84-9.00 (1H, m) 3.58 (3H, s), 4.02-4.36 (2H, m), 7.91 (1H, t, .. C 50.23, H 8.79, N 9.25 NMR (DMSO-d6, 6): 1.04-1.10 (3H, m), 1.20-1.83 Elemental Analysis $C_{1gH}23N_3O_4 \cdot HC1 \cdot 2 \cdot 8H_2O$ (%) carbonyl]-3-methyl-\$-alanine methyl ester hydrochloride

20

Mass (m/z): 368 (M^++1) free of compound

: C 50.36, H 6.51, N 8,97

Found

piperidylcarbonyl]+β-alanine benzyl ester N-{(R)-1-{3-(4-piperidyl)propionyl}-3-IR (Film): 3400, 1710, 1630 cm-1 hydrochloride 3

30

NMR (DMSO-d6, 6) : 1.17-1.91 (12H, m), 2.29-2.36

.3.70-3.83 (1Н, m), 4.20-4.37 (1Н, m), 5.09 (2Н, "(3H, m), 2.56-3.09 (4H, m), 3.17-3.33 (5H, m);

35

s), 7.31-7.38 (5H, m), 7.99-8.14 (1H, m), 8.60-C 54.23, H 7.54, N 7.88 Calcd. : C 54.26, H 7.63, N 7.91 Mass (m/z): 430 (M^++1) free of compound Elemental Analysis $C_{24}H_{35}N_{3}O_{4}HCl \cdot 1.6H_{2}O$ 8.72 (1H, br), 8.89-8.99 (1H, br) Found

NMR (DMSO-d6, 6): 1.15-1.53 (13H, m), 1.44 (3H, d, IR (Film) : 3380, 2940, 2850, 1740, 1630 cm⁻¹ piperidylcarbonyl]-\balanine 1-(cyclohexyloxy-(4) N-[(R)-1-{3-(4-piperidyl)propionyl}-3carbonyloxy)ethyl ester hydrochloride

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8.00-8.13 (1H, m), 8.47-8.64 (1H, br), 8.79-8.90 J=5.4Hz), 1.60-1.92 (10H, m), 2.05-2.39 (3H, m), 2.46-3.08 (5H, m), 3.18-3.30 (4H, m), 4.15-4.37 (1H, m), 4.50-4.60 (1H, m), 6.60-6.68 (1H, m), (1H, br)

15

C 52.04, H 8.40, N 7.00 C 51.85, H 8.51, N 7.14 Mass (m/z): 510 (M^++1) free of compound Elemental Analysis $C_{26H_43N_3O_7\cdot HCl\cdot 3H_2O}$ Calcd. : Found

20

NMN (DMSO-d6, 8): 1.18 (3E, t., J=7.0Hz), 1.27-2.02 Pircijdylcarbonyl:}-3-piperidin⊖carboxylic.acid:ethyl (5) (R)-[1-{3-(4-piperidyl)propionyl}-3-PS* :: trif],uoro acètate

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3.67-3.91 (2H, m), 4.07 (2H, q, J=7.0Hz), 4.20-(16H, m), 2.23-2.43 (3H, m), 2.57-3.15 (7H, m), 4.40 (1H, m), 4.54-4.75 (2H, m), 8.09-8.34 (1H, br), 8.51-8.65 (1H, br)

Mass (m/z): 408 (M^++1) free of compound

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piperidylcarbony.]-2-phenyl- β -alanine ethvl ester. (6) N-[(R)-1-{3-(4-piperidyl)propionyl}.3hydrochloride

IR (KBr, pellet) : 3421, 2943, 1728, 1643, 1624 cm-1 3.32-3.75 (3H; m), 3.80-3.92 (1H, m), 3.99-4.34 (3H, m), 2.69-3.06 (3H, m), 3.13-3.25 (2H, m), (4H, m), 7.20-7.38 (5H, m), 8.07-8.20 (1H, m), NMR (DMSO-d6, 8): 1.05-1.85 (14H, m), 2.04-2.34 8.75-8.90 (1H, br), 9.04-9.15 (1H, br) Mass (m/z) : 444 (M^++1) free of compound

Piperidylcarbonyl]-3(S)-ethynyl- β -alanine 2-adamantyl (7) N-[(R)-1-{3-(4-piperidyl)propionyl}-3ester hydrochloride

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IR (Nujol): 1720, 1650, 1600 cm-1

(4H, m), 4.83-4.95 (2H, m), 8.50 and 8.60 (total 3.09-3.29 (3H, m), 3.69-3.84 (1H, m), 4.15-4.55 (15H, m), 2.10-2.39 (3H, m), 2.59-3.02 (5H, m), NMR (DMSO-d6, 6): 1.18-1.60 (8H, m), 1.70-1.99 1H, d, J=8.1 and 8.2Hz), 8.72-8.89 (1H, br), 9.03-9.12 (1H, br)

15

C 59.57, H 8.64, N 7.03 Calcd. : C 59.58, H 8.55, N 7.19 Mass (m/z): 498 (M^++1) free of compound Elemental Analysis $C_{29}H_{43}N_3O_4 \cdot HCl \cdot 28H_2O$ 一五四面的 Found 17.

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- IR (KBr, pellet) =: 2958, 2872, 1734, 1647, 1616 cm-1 Piperidylcarbonyl 33(5)-ethynyl-g-alanine-n-butyl. (8). N-[(R)-1-43-(4-piperidy1)propiony1}-3ester hydrochloride

25

: (12H, m), 1:59 (1H, d, J=2.4Hž); 1.75-1.86 (3H, m), 2.08-2.40 (3H, m), 2.60-3.08 (6H, m), 3.17-(total (1H; d, J=8.3 and 8.0Hz), 8.74-8.86 (1H, 3.27 (3H, m), 3.69-3.84 (1H, m), 4:03 (2H, t, J=6.5Hz), 4.79-4.92 (1H7-m), 8.50 and 8.59 Elemental Analysis $C_{23H_37N_3O_4\cdot HCl\cdot 1.6H_2O}$ br), 9.02-9.13 (1H, br)

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Calcd. : C 56.98, H 8.56, N 8.67 C 56.99, H 8.63, N 8.39 Found

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piperidylcarbonyl]-3(S)-ethynyl- β -alanine 5-methyl-2oxo-1,3-dioxol-4-yl-methyl ester hydrochloride (9) N-[(R)-1-{3-(4-piperidy1)propiony1}-3-.D.02 : dw

IR (KBr, pellet) : 2947, 2866, 2729, 1817, 1743, 1653, 1616 cm⁻¹

9

8.62 (total lH, d, J=8.0Hz), 8.76-8.90 (lH, br), (3H, m), 2.10 (3H, s), 2.60-3.09 (5H, m), 3.13-3.29 (3H, m), 3.70-3.84 (1H, m), 4.79-4.91 (1H, m), 4.98 (2H, s), 5.12-5.40 (2H, m), 8.53 and NMR (DMSO-d6, 6): 1.29-1.85 (11H, m), 2.09-2.40 9.03-9.15 (1H, br)

Mass (m/z): 476 (M^++1) free of compound

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3.19-3.26 (3H, m), 3.83 (2H, d, J=6.5Hz), 4.13-(12H, m), 1,99-2.37 (3H, m), 2.60-3.02 (6H, m), NWR (DMSO-d6, 8): 0.89 (6H, d, J=6.6Hz), 1.21-1.91 Piperidylcarbonyl]-3(S)-ethynyl- β -alanine isobutyl IR (KBr, pellet) : 3446, 3230, 3030, 2960, 2873, 1734, 1653, 1616 cm⁻¹ (10) N-[(R)-1-{3-(4-piperidyl)propionyl}-3ester hydrochloride

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4.32 (2H, m), 4.80-4.94 (1H, m), 8.46-8.57 (1H,

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m), 8.53-8.71 (1H, br), 8.89-9.00 (1H, br)

Mass.(m/z) : 420 (M⁺+1) free of compound.

IR (KBr, Pellet) : 3456, 3240, 2947, 2864, 2360, piperidylcarbonyl]-3(S)-ethynyl-β-alanine-4trifluoromethylbenzyl ester hydrochloride (11) $N-[(R)-1-\{3-(4-p), peridy1\}\}-3-$

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1.17-1.86 (12H, m), 2.06-2.36 1740, 1653, 1618 cm⁻¹ NMR (DMSO-d6, 6) :

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4.07-4.35 (1H, m), 4.85-4.96 (1H, m), 5.22 (2H, (3H, m), 2.60-3.06 (6H, m), 3.12-3.31 (3H, m), s), 7.60 (2H, d, J=8:2Hz), 7.76 (2H, d,

J=8.2Hz), 8.48-8.58 (1H, m), 8.44-8.58 (1H, br), 8.74-8.85 (1H, br)

Mass (m/z): 522 (M^++1) free of compound

piperidylcarbonyl]-2(S)-acetylamino-\0-alanine ethyl (12) N-[(R)-1-{3-(4-piperidyl)propionyl}-3ester hydrochloride

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IR (KBr, pellet) : 2947, 2862, 1718, 1697, 1684, 1668 cm⁻¹

NMR (DMSO-d6, 6): 1.17 (3H, t, J=7.1Hz), 1.24-1.69 2.59-3.11 (4H, m), 3.15-3.28 (2H, m), 3.31-3.37 J=7.1Hz), 4.15-4.31 (2H, m), 8.12-8.43 (2H, m), (9H, m), 1.74-1.99 (4H, m), 2.07-2.40 (4H, m), (2H, m), 3.73-3.86 (1H, m), 4.02 (2H, g, 8.63-8.75 (1H, br), 8.93-9.04 (1H, br)

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Mass (m/z): 425 (M^++1) free of compound

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piperidylcarbonyl]-2(S)-acetylamino-0-alanine benzyl IR (Rbr) : 3377, 2945 3 2 2 4 6 4 5 2 7 3 1 7 4 0 7 1 6 5 3 , (13) N-[(R)-1-{3-(4-piperidyl)propionyl}-3-The second 6080 cm 7 the separation at the Principle at the Princip ester hydrochloride

(cyclohexyloxycarbonyloxy)ethyl ester hydrochloride piperidylcarbony]-2(S)-acetylamino- β -alanine 1-IR (KBr) : 3417, 3062, 2945, 2862, 1961, 1653, (14) (N-F(R)-1+(3-(4-piperidy1)propiony1}-3-1608 cm-1

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Example 26

(1) To a solution of $N-[2-[1-\{3-(1-tert-butoxycarbonyl-4$ piperidy:1)propiony1}-4-piperidyl]acety1]-\$-alanine methy1

3

The organic layer was separated and washed with brine, and ambient temperature and evaporated in vacuo to give N-[2into a mixture of ethyl acetate (20 ml) and water (10 ml) and acidified to pH 3.0 with 10
m \$ KHSO $_4$ aqueous solution. dried over MgSO $_4$. The solution was evaporated in vacuo. The residue was dissolved with ethyl acetate (5 ml) and The resultant mixture was stirred for 1 hour at The resultant mixture was poured the solution of 4N HCl in ethyl acetate (3.1 ml) was [1-{3-(4-piperidy1)propiony1}-4-piperidy1]acety1]-\$aqueous solution (1.5 ml) and stirred for 1 hour at ester (0.58 g) in methanol (7 ml) was added IN NaOH alanine hydrochloride (0.2 g). ambient temperature. added.

NMR (DMSO-d6, 5): 0.95-1.14 (1H, m), 1.21-1.62 (7H, m), 1.76-1.83 (2H, m), 2.26-2.40 (4H, m), 2.75-3.00 (3H, m), 3.17-3.24 (5H, m), 3.78-3.84 (2H, m), 4.05-4.08 (1H, m), 4.28-4.35 (2H, m), 7.93-7.97 (1H, m), 8.70 (1H, br), 8.95 (1H, br)

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The following compounds were obtained according to a similar manner to that of Example 26 (1)

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(2) N-[1-{3-(4-Piperidyl)propionyl}-3-piperidylearbonyl]-N-methyl-β-alaning hydrochloride

NMR (DMSO-d6, 6): 1.39-1.45 (7H, m), 1.59-1.83 (5H,-3.02 (total 3H, s), 3.00-3.23 (3H, m), 3.40-3.80 m), 2.36-2.60 (4H, m), 2.69-2.88 (2H, m), 2.77, (3H, m), 4.30-4.40 (1H, m), 8.76 (1H, br), 9.00 (1H, br)

Mass (m/z) : 354 (M+1)

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piperidylcarbonyl]-3(S)-[2-(3-indolyl)ethyl] $-\beta-$ (3) N-[(R)-1-{3-(4-piperidyl)propionyl}-3alanine hydrochloride

IR (Nujol): 3200, 1720, 1630, 1610, 1540 cm-1

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NMR (DMSO-d₆, 6) : 1.14 (1H, t, J=7.0Hz), 1.21-1.45 2.60-3.00 (6H, m), 3.19-3.25 (3H, m), 3.78-4.33 J=8.0Hz), 7.47 (1H, d, J=8.0Hz), 7.90-7.96 (1H, (5Н, т), 1.65-1.91 (6Н, т), 2.10-2.42 (3h, т), Calcd. : C 57.89, H 7.99, N 8.71 C 57.97, H 8.16, N 8.31 (7H, m), 6.91-7.08 (3H, m), 7.32 (1H, d, Mass (m/z): 483 (M^++1) free of compound Elemental Analysis $\mathtt{C}_{\mathsf{27H}_{\mathsf{38N}_{\mathsf{4}}\mathsf{0}_{\mathsf{4}}}$ HCl $_{\mathtt{2}}\mathtt{H}_{\mathsf{2}\mathsf{0}}$ m), 8.58 (1H, br), 8.84 (1H, br) Found:

piperidylcarbonyl]-3(S)-vinyl- β -alanine hydrochloride 3.82-4.38 (4h, m), 4.54-4.62 (1H, m), 5.05-5.12 (5H, m), 2.75-3.00 (2H, m), 3.19-3.24 (2H, m), (2H, m), 5.74-5.92 (1H, m), 8.00-8.06 (1H, m) NMR (DMSO-d6, 6): 1.17-1.99 (11H, m), 2.32-2.60 IR (KBr) : 3428, 2946, 1724, 1629, 1621 cm-1 Mass (m/z): 366 (M^++1) free of compound (4) N-[(R)-1-{3-(4-piperidy1)propiony1}-3-

-1,21-1,91 (14H, m), 2,18#2;40i(5H, m), 2,59-3,23 $\label{eq:piperidylcarbonyl} $$ piperidylcarbonyl]-3(S)-ethyl-\beta-alanine \ hydrochloride$ NMR (DMSO-d6/、5)..: 0{76-0:83 (3H, t, 0,463,3Hž) ゆう (5H, m), 3:76-4.35/(3Bpmm);ppdp:07=7:83 (1H, m) IR.(KBr) : 3407, 3257, 1724, 1637 cm-1 Mass (m/z): 368 (M*+1) wfree of compound (5) N-[(R)-1-{3-(4-piperidyl)propionyl}-3-· Callette Control

25

NMR (DMSO-d6, 5): 1.20-1.82 (12H, m), 1.85 (3H, s), 2.10-2.43 (5H, m), 2.59-3.27 (4h; m), 3.74-3.83 (2H, m), 4.14-4.37 (2H, m), 8.02-8.19 (2H, m), carbonyl]-2(S)-acetylamino-A-alanine hydrochloride (6) N-[(R)-1::{3-(4-piperidyl)propionyl}-3-piperidyl-IR (Nujoi) : 1720, 1640, 1610 cm-1 $||\alpha||_{S}^{5} = -21.37^{\circ} (C=0.75, MeOH)$

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8.42-8.59 (1H, br), 8:72-8.84 (1H, br)

NMR (DMSO-d6, 5): 1.21-1.30 (4H, m), 1.76-1.83 (2H, m), 2.00-2.12 (2H, m), 2.23-2.50 (2H, m), 2.57-2.61 (2H, m), 2.76-3.06 (4H, m), 3.18-3.25 (4H, (7) N-[1-{3-(4-piperidyl)propionyl}-3-pyrrolidinylcarbonyl]-3(S) ethynyl-β-alanine hydrochloride m), 3.50-3.60 (6H, m), 4.81-4.85 (1H, m) Mass (m/z): 397 (M^++1) free of compound Mass (m/z) : 350 (M^++1) free of compound

10

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NMR (D₂O, 8) : 1.05 (3H, d, J=7.2Hz), 1.33-1.76 (8H, m), 1.90-1.98 (3H, m), 2.32-2.57 (4H, m), 2.76-3.01 (3H, m), 3.11-3.42 (5H, m), 3.79-3.90 (1H, (8) N-[(R)-1-{3-(4-piperidyl)propionyl}-3piperidylcarbonyl]-2-methyl-ß-alanine m), 4.12-4.30 (1H, m) Mass (m/z) : 354 (M⁺+1)

13

Example 27

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concentrated in vacuo and freeze-dried to give N-[(R)-1- \sim water and desalted by DIAION HP-20 (trademark; prepared by carbony]]-3(S)ethynyl- β -alanine trifluoroacetate (object compound (I) of Example 25) (30.0 g) was dissolved in N-[(R)-1-{3-(4-Piperidyl)propionyl}-3-piperidyl-{3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-(isopropanol: $H_2O=1:3$). The eluting solution was Mitsubishi chemical Industries) eluting with ethynyl-b-alanine (49.8 g) as a whits solid. IR (KBr) : 3430, 3270, 1722, .622 cm-1

25

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NMR (DMSO-d6, 6) : 1.23-2.06 (11H, m), 2.30-2.35 (4H, m), 2.52-2."3 (4H, m), 2.98-3.17 (4H, m), 3.01 (1H, d, J=2.2.3), 3.53-3.59 (1H, m), 4.21-4.27 (1H, m), 4.68-4.72 (1H, m), 8.28-8.40 (1H, m) Mass (m/z): 364 $(M^{+}+1)$

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Elemental Analysis C₁₉H₂₉N₃O₄·1.7H₂O (%)
Calcd.: C 57.91, H 8.29, N 10.66
Found: C 57.89, H 8.05, N 10.41

Example 28

A solution of N-[(R)-1-{3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-ethynyl-\$\theta-alanine hydrochloride (89.6 g) in water (900 ml) was purified by HPLC (C-18, 7 x 50 cm) eluting with a solution of 17% CHJCN in 0.1% TFA aqueous solution and the fractions containing object compound were combined and evaporated in vacuo. The residue was dissolved in water and desalted by HP-20 eluting with (IPA:water = 1:3). The eluting solution was concentrated in vacuo and freeze-dried to give N-[(R)-1-{3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-ethynyl-\$\theta-alanine (55.8 g) as a white solid.

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IR (KBr): 3430, 3270, 1722, 1622 cm⁻¹

NMR (DMSO-d₆, 6): 1.23-2.06 (11H, m), 2.30-2.35 (4H, m), 2.52-2.70 (4H, m), 2.98-3.17 (4H, m), 3.01 (1H, d, J=2.2Hz), 3.53-3.59 (1H, m), 4.21-4.27 (1H, m), 4.68-4.72 (1H, m), 8.28-8.40 (1H, m)

20

Elemental Analysis $C_{19}H_{29}N_{3}O_{4}\cdot 1\cdot 7H_{2}O$

Calcd. : C 57.91, H 8.29, N 10.66 Pound : C 57.89, H, 8.05; N 10.41

Example 29

22

A solution of N-[(R)-14/3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-3-phenyl-\$-alanine hydrochloride in water (30 ml) was-purified by HPLC on C16 Silica geleluting with 10.1% TFA aqueous solution:CH3CN = 44:11) to give N-[(1R)-1-{3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-phenyl-\$-alanine trifluorcacetate (0.08 g) as an oil.

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 $[\alpha]_0^2 = -39.62^\circ$ (C=0.45, MeOH)

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IR (Film): 2910, 2850, 1710, 1630 cm-1

NMR (DMSO-d6, 5): 1.17-1.85 (11H, m), 2.12-2.36

(2+1/2H, m), 2.60-3.28 (7+1/2H, m), 3.71-3.83

(1H, m), 4.12-4.38 (2H, m), 5.18 (1H, q,

J=7.8Hz), 7.20-7.38 (5H, m), 8.18-8.32 (1H, br),

8.42 (1H, d, J=8.3Hz), 8.54-8.64 (1H, br)

Mass (m/z): 416 (M*+1) free of compound

and

N-[(R)-1-{3-(4-piperidyl)propionyl}-3piperidylcarbonyl]-3(R)-phenyl-β-alanine trifluoroacetate
(0.08 g) as an oil

10

[\alpha]\$\beta\$ = -1.20° (C=1.0, MeOH)\$

IR (Film) : 3250, 2960, 1710, 1600 cm⁻¹

NMR (DMSO-d₆, \beta) : 1.12-1.85 (11H, m), 2.11-2.36

(3H, m), 2.66 (2H, d, J=7.5Hz), 2.79-3.11 (3H, m), 3.17-3.29 (2H, m), 3.63-3.84 (1H, m), 4.11-4.33 (2H, m), 5.11-5.23 (1H, m), 7.24-7.34 (5H, m), 8.07-8.23 (1H, br), 8.40 (1H, d, J=8.1Hz), 8.40-8.53 (1H, br)

The following compound was obtained according to similar manners.to:that of Example 13 (1) and Example 21 (1).

Mass (m/z): 416 (M^++1) free of compound

20

Example 30

N-[(R)-1-(3-(4-piperidyl)propionyl)-3piperidylcarbonyl]-2-benzyl-\$-alanine hydrochloride
IR :KBr, pellet): 3439, 2941, 1724, 1639, 1618 cm⁻¹
NMR (DMSO-d₆, 6): 1.21-1.86 (11H, m), 2.09-2.40
(3H, m), 2.55-2.89 (6H, m), 2.93-3:25 (5H, m),
3.72-3.86 (1H, m), 4.12-4.41 (1H, m), 7.17-7.31
(5H, m), 8.04-8.20 (1H, m), 8.71-8.86 (1H, br),
9.00-9.14 (1H, br),

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- 153

Mass (m/z): 430 $(M^{+}+1)$ free of compound

similar manners to that of Example 13 (1) and Example 21 The following compound was obtained according to $\dot{\exists}$

Example 31

3.68-3.91 (2H, m), 4.27-4.40 (2H, m), 8.68-8.86 (3H, m), 2.57-3.11 (5H, m), 3.13-3.25 (2H, m), NMR (DMSO-d6, 6) : 1.18-1.99 (17H, m), 2.17-2.40 N-[(R)-1-{3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-3-piperidynecarboxylic acid hydrochloride Mass (m/z): 380 (M^++1) free of compound (1H, br), 8.99-9.11 (1H, br)

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similar manners to that of Example 13 (1) and Example 21 The following compound was obtained according to Ė

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Example 32

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IR (KBr, pellet) : 3410, 3392, 2947, 1724, 1535, piperidylcarbonyl -2-phenyl-\beta-alanine hydrochloride N-[(R)-1-{3-(4-piperidyl)propionyl}-3-1616 cm-1

3.31-3.84 (4H, m), 4.11-4.34 (1H, m), 7.24-7.33 (5H, m), 8.01-8.15 (1H, m), 8.73-8.85 (1H, bz), (4H, m), 2.69-3.06 (3H, m), 3.16-3.27 (2H, m), NMR (DMSO-d6, 6): 1.21-1.86 (11H, m), 2.04-2.61 Mass (m/z): 416 (M^++1) free of compound 9.00-9.12 (1H, br)

25

manners to that of Example 13 (1) and Example 21 (1): The following compound was obtained to similar

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Example 33

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 $\texttt{piperidylcarbonyl} \\ \texttt{-} \\ \texttt{N-methyl-} \\ \texttt{\beta-alanine} \ \texttt{trifluoroacetate}$ IR (KBr, pellet) : '3419, 2951, 2866, 1724, 1680, N-[(R)-1-{3-(4-piperidy1)propiony1}-3-1.620 cm⁻¹

m), 4.26-4.40 (1H, m), 8.14-8.27 (1H, br), 8.47-(3H, m), 2.70-3.15 (5H, m), 2.78 (3H, s), 3.20-3.32 (2H; m), 3.40-3.62 (2H, m), 3.73-3.88 (1H, NMR (DMSO-d6, 6): 1.14-1.91 (12H, m), 2.11-2.44 8.59 (1H, br)

Mass (m/z): 354 (M^++1) free of compound

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Example 34

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To a solution of $N-[(R)-1-\{3-(1-text-butoxycarbony1$ dissolved in water and freeze-dried to give $(S)-4-[\,(R)-1$ dichloromethane (3 ml) was added trifluoroacetic acid (3 1,2,3,4-tetrahydro-2-furanone (0.17 g) as a pale yellow ml) at ambient temperature. After stirring for 1 hour, the mixture was evaporated in vacuo. The residue was {3-(4-piperidyl)propionyl}~3-piperidylcarbonylamino}hydroxymethyl- β -alanine tert-butyl ester (0.2 g) in 4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-

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3.32 (1H, m), 4.17-4.34 (2H, m), 4.61-4.82 (2H, m) m), 2.81-3.10 (4H, m), 3.17-3.44 (3H, m), 3.77ла (р20, в) : 1.30-2.22 (ПЕ. т), 2.44-2.62 (4H, . IR (KBr) : 3425, 1776, 1678, 1624, 1549 cm-1 Mass (m/z): 352 (M^++1) free of compound

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Example 35

alanine tert-butyl ester (460.º mg) in dichloromethane (5 (I) Mr. a solution of N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-piperidyl)propionyl}-3-piperidy\ca \pm bonyl]-3(S)-cyano- β stirring at ambient temperature for 2 hours, the mixture was concentrated in vacuo. The residue was dissolved in ml.) was added trifluoroacetic acid (4.6 ml). After

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water and desalted by HP-20 eluting with (IPA:water = 1:1). The eluting solution was concentrated in vacuo and freeze-dried to give N-[(R)-1-{3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-cyano-β-alanine (0.12 g).

 $\{\alpha\}_0^{20} = -31.63^\circ$ (C=1.0, MeOH) IR (Film) : 3400, 2950, 2850, 1680, 1620 cm⁻¹ NMR (DMSO-d₆, 5) : 0.96-1.82 (13H, m), 2.33-2.82 (6H, m), 2.90-3.34 (4H, m), 3.71-3.89 (1H, m),

4.21-4.47 (1H, m), 6.89-7.35 (1H, m) Mass (m/z) : 365 (M⁺+1)

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The following compounds were obtained according to a similar manner to that of $\overline{\text{Example }35}$ (1).

(2) N-[(R)-1-{3-(4-piperidyl)propionyl}-3piperidylcarbonyl]-3(S)-(n-butanesulfonylaminomethyl)-\beta-alanine trifluoroacetate
IR (Nujol): 1730 cm
IR (Nujol): 0.88 (3H, t, J=7.2Hz), 1.29-1.43

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(14H, m), 1.78-1.84 (3H, m), 2.30-2.38 (3H, m), 2.60-2.64 (2H, m), 2.75-3.10 (8H, m), 3.22-3.28 (2H, m), 3.70-3.80 (1H, m) Mass (m/z): 489 (M+1) fige of compound

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(3; 4-[3-(4-piperidyl)propionylamino³1-piperidyl]-4-oxo-2(S)-benzoylamino-butyric acid IR (XBr, pellet): 3061, 2945, 2862, 1716, 1647,

MMR (DMSO-d₆, δ) : 1.04-1.83 (8H, m), 2.03-2.46 (2H, m), 2.60-2.78 (2H, m), 3.09-4.80 (13H, m), 4.98-5.23 (1H, m), 7.34-7.54 (3H, m), 7.84-7.94 (2H, m), 8.20-8.89 (1H, m)

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Mass (m/z) : 489 (M⁺+1)

Example 36

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(1) A mixture of N-[(R)-1-{3-(4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-ethynyl-β-alanine trifluoroacetate (0.57 g) and 4.9 HCl in ethanol (30 ml) was stirred at ambient temperature for 2 hours, and the mixture was evaporated in vacuo. The residue was purified by HPLc on Cl8 silica gel eluting with a solution of 18% CH₃CN in 0.1% aqueous TFA solution, and the fractions containing object compound were combined and evaporated in vacuo and freeze-dried to give N-[(R)-1-{3-(4-piperidyl)propionyl}-3-piperidyl]-3(S)-ethynyl-β-alanine ethyl ester trifluoro acetate (0.52 g).

[d]\$\frac{1}{6}\$ = -25.60° (C=1.0, MeOH)\$

IR (Film) : 3280, 2930, 2850, 1760, 2720, 1630 cm^-1

NWR (DMSO-d6, 6) : 1.18 (3H, t, J=7.1Hz), 1.26-1.84

(10H, m), 2.09-2.19 (3H, m), 2.55-3.28 (9H, m),

2.66 (1H, d, J=7.5Hz), 3.68-3.82 (1H, m), 4.08

(2H, q, J=7.1Hz), 4.13-4.31 (1H, m), 4.79-4.93

(1H, m), 8.10-8.63 (3H, m)

Mass (m/z) : 394 (M+1) free of compound

The following compound was obtained according to similar manner to that of Example 36 [1].

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(2) N-[(R)-1-{3·(4-piperidyl)propionyl}-3-piperidylcarbonyl]-Z-benzyl-A-alanine ethyl estertifiluoroacetate IR (KBr, pellet): 2945, 2862, 1726, 1680, 1647,

1624 cm⁻¹
NMR (pMSO-d₆, 6): 1.06 (3H, t, J=7.1Hz), 1.15-1.66

(7½, m), 1.75-1.87 (4H, m), 2.07-2.39 (3H, m), 2.71-2.95 (64, m), 3.09-3.32 (5H, m), 3.68-3.84 (1H, m), 3.96 (2H, q, J=7.1Hz), 4.10-4.39 (1H, m), 7.14-7.39 (5H, m), 8.01-8.10 (1H, m), 8.16-8.30 (1H, br), 8.48-8.60 (1H, br)

Mass (m/z): 458 (M+1) free of compound

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Example 37

alanine (0.61 g) in N.N-dimethylformamide (6 ml) was added potassium carbonate (182 mg) under stirring at $0^{\circ}\mathrm{C}$. After stirring at 0°C for 15 minutes, isopropylbromide (0.91 ml) $piperidyl)propionyl\}-3-piperidylcarbonyl]-3(S)-ethynyl-\beta$ gel eluting with (CHCl3:MeOH = 100:1) to give N-[(R)-1-{3-(1) To a solution of N-[(R)-1-(1-tert-butoxycarbonyl-4-Piperidylcarbonyl]-3(S)-ethynyl- β -alanine isobutyl ester residue was purified by column chromatography on silica saturated agueous ammonium chloride, and extracted with brine, and dried over ${
m MgSO}_4$, and evaporated in vacuo. ethyl acetate. The extract was washed with water and was added to the mixture. After stirring at ambient temperature for 3 days, the mixture was poured into (1-tert-butoxycarbonyl-4-piperidyl)propionyl}-3-(0.63 g) as an oil.

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(2H, m), 1.45 (9H, s), 1.40-1.75 (8H, m), 1.92-(total 3H.m), 5:5:05-5:15 (1H, m), 6:64-6.71 and 2.02 (3H, m), 2.27 (1H, d, J=2.2Hz), 2.32-2.40 (3H, m), 2.61-2.73 (4H, m), 3.20-3.63 (2h, m), 3.90 (2H, d, J=6.4Hz), 3.83-4.15 and 4.35-4.47 NMR (CDCl₃, 6): 0.95 (6H, d, J=6.7Hz), 1.01-1.22 IR (Film) : 2920, 1720, 1660, 1620 cm-1 Staff (1997, 103 (total 1H, m) Mass (m/z): 520 (M++1)

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The following compounds were obtained according to a similar manner to that of Example 37 (1)

:5.25.25.

ethynyl-eta-alanine 5-methyl-2-oxo-1,3-dioxol-4-yl-IR (Film) : 3000, 2920, 2850, 1810, 1740, 1640, piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-(2) N-[(R)-1-{3-(1-tert-butoxycarbony1-4methyl ester

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1.53-2.10 (11H, m), 2.19 (3H, s), 2.30-2.36 (4H, 3.20-3.61 (2H, m), 3.99-4.15 (2H, m), 4.88 (2H, NMR (CDCl₃, 8): 1.02-1.23 (2H, m), 1.45 (9H, s), m), 2.60-2.81:(3H; m), 2.73 (2H, d, J=5.7Hz), s), 6.95-7.04 (1H, m) Mass (m/z): 576 $(M^{+}+1)$

s), 7.35-7.51 (10H, m), 7.80-7.95 (1H, m), 8.03- $\tt propiony1\}-3-piperidylcarbony1]-2(S)-benzoylamino-\beta-$ J=5.8Hz), 2.30-2.52 (ЗН, м), 2.64-2.80 (1H, м), 4.07-4.21 (2H, m), 4.57-4.83 (1H, m), 5.12 (2H, NMR (CDCl3, 5): 0.99-2.00 (30H, m), 1.83 (3H, d, alanine 1-(cyclohexyloxycarbonyloxy)ethyl ester (3) N-[(R)-1-{3-(1-benzyloxycarbonyl-4-piperidyl)-IR (Film) : 2920, 2950, 1740, 1680, 1650 cm⁻¹ Mass (m/z): 763 (M^++1) 8.09 (1H, m)

m), 2.27-2.36 (4H, m), 2.62-2.77 (4H, m), 3.33-1.45 (9H, s), 1.56-1.70 (5H, m), 1.88-2.05 (5H, 3.53 (2H, m), 4.07-4.18 (3H, m), 5.08-5.13 (1H, NWR (CDC13, 6): 1.09-1.21 (2H, m), 1.23 (9H, S), (4) N-[(R)-1-{3-(1-tert-butoxycarbony1-4-piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-ethynyl- β alanine pivaloyloxymethyl ester

m), 5.77 (2H, s), 7.01-7.04 (1H, m) Mass (m/z) : 578 (M⁺+1)

2.19-2.51 (4H, m), 2.59-2.74 (2H, m), 3.21-3.43 1.35-1.77 (7H, m), 1.99 (2H, s), 2.08 (3H, s), NMR (CDCl3, 6): 1.03-1.72 (2H, m), 1.45 (9H, s); Piperidyl)propionyl}-3-piperidylaarbonyl]-2(S)-IR (Film) : 2926, 2850, 1730, 1650, 1620 cm-1 (5) N-[(R)-1-{3-(1-tert_butoxycarbonyl-4acetylamino-8-alenine benzyl ester

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4.64-4.85 (1H, m), 5.00-5.18 (2H, m), 7.06-7.19 (2H, m), 3.47-3.89 (ZH, m), 4.03-4.21 (3H, m), (lh, m), 7.32÷7.40 (6H, m)

s), 2.14-2.53 (4H, m), 2.60-2.76 (2H, m), 3.12-WAR (CDCl3, 6): 1.00-1.23 (2H, m), 1.28-1.80 (21H, 3.33 (2Н, m), 3.41-3.80 (2Н, m), 4.02-4.14 (2Н, m), 4.25-4.44 (1H, m), 4.57-4.71 (1H, m), 6.60m), 1.45 (9H, s), 1.86-1.98 (3H, m), 2.04 (3H, propionyl}-3-piperidylcarbonyl]-2(S)-acetylamino-β-(6) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-piperidyl)-IR (Film) : 2930, 2855, 1740, 1650, 1620 cm⁻¹ alanine 1-(cyclohexyloxycarbonyl)ethyl ester 6.69 (1H, m), 7.28-7.40 (1H, m)

Example 38

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carbodiumide hydrochloride (0:32 g) under stirring at overnight, the solution was evaporated in vacuo. " "he ethyl acetate. The extract was washed with saturated over MgSO4, and evaporated in vacuo. The residue was (1) To a mixture of $N-[(R)-1-\{3-(1-text-butoxycarbonyl-4$ dimethylaminopyridine (18 mg) in dichloromethane (7 aqueous NaHCO3 solution, water and brine, and dried eluting with (CHCl₃:MeOH = 100:1) to give N-[(R)-1-(trifluoromethyl)benzyl alcohol (0.23 ml) and N,N-(3-(1-tert-butomycarbonyl-4-piperidyl)propionyl}-3-'tresidue was poured into water and extracted with ml) was added 1-ethyl-3-(3-dimethylaminopropyl)-0.C. Miter stirring at ambient temperature for purified by column chromatography on silica gel triflingromethylbenzyl ester (0.71 g) as an oil μiperidylcarbonyl]-3(S)-ethynyl-β-alanine 4-IR (Film) : 2920, 2850,1730, 1650, 1620 cm⁻¹ piperidyl)propionyl}-3-piperidylcarbonyl}-3(S)ethymyl- β -alanine (0.63 g), 4-25

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d, J=8.4Hz), 7.49 (2H, d, J=8.1Hz), 7.63 (2h, d, 1.43-1.72 (7H, m), 1.84-2.12 (2H, m), 2.28 (1H, 3.50-3.64 (1H, m), 3.98-4.16 (3H, m), 5.08-5.24 (1H, m), 5.20 (2H, s), 6.61 and 7.04 (total 1H, d, J=2.4Hz), 2.31-2.39 (3H, m), 2.60-2.90 (2H, m), 2.77 (2H, d, J=5.8Hz), 3.19-3.42 (2H, m), NMR (CDCl₃, 8): 1.01-1.22 (2h, m), 1.45 (9H, s), J=8.2Hz)

Mass (m/z) : 622 (M^++1)

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The following compounds were obtained according to similar manner to that of Example 38 (1)

(2H, m), 1.31-1.77 (11H, m), 1.45 (9H, s), 1.86-3.52-3.66 and 3.85-4.00 (total 1H, m), 4.12 (2H, 2.11 (2H, m), 2.28 (1H, d, J=2.3Hz), 2.32-2.40 (3H, m), 2.60-2.80 (4H, m), 3.20-3.41 (2H, m), t, J=6.6Hz), 4.05-4.71 (3H, m), 5.05-5.16 (1H, NMR (CDCl3, 6): 0.94 (3H, t, J=7.2Hz), 1.01-1.22 piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-IR (Film) : 2910, 2850, 1720, 1650, 1620 cm-1 m), 6.67-6.75 and 7.00-7.05 (total 1H. m) (2) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4ethynyl-ß-alanine n-butyl ester Mass (m/z): 520 (M^++1)

1.35-1.63 (7H, m), 1.74-1.93 (9H, m), 2.00-2.05 3.20-3.40 (2H, m), 3.54-3.66 (1H, m), 3.85-3.98 (4H, m), 2.27-2.39 (4H, m), 2.61-2.81 (5H, m), (1H, m), 4.05-4.16 (2H, m), 4.37-4.50 (1H, m), NMR (CDC13, 8) : 1.01-1.21 (2H, m), 1.45 (9H, s), ... piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-(3) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4ethynyl-ß-alanine 2-adament; Lester IR (Nujol) : 1720, 1660; 1625 cm-1

4.97-5.03 (1H, m), 5:07-5.17 (1H, m), 6.70-6.78 (1H, m), 6.99-7.08 (1H, m) Mass (m/z) : 598 (M^++1)

Example 39

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To a solution of N-[(R)-1-{3-(4-piperidy1)propiony1}hydrochloride (0.47 g) in N,N-dimethylformamide (5 ml) was stirring at ambient temperature for overnight, the mixture extracted with ethyl acetate. The extract was washed with on silica gel eluting with (CHCl $_3$:MeOH = 100:1) to give Ndimethylformamide (1 ml) was added to the mixture. After vacuo. The residue was purified by column chromatography added potassium carbonate (0.2 g) under stirring at $0^{\circ}\mathrm{C}.$ was poured into saturated aqueous ammonium chloride, and $piperidyl\}propionyl]-3-piperidylcarbonyl]-3(S)-ethynyl-\beta$ water and brine, and dried over $MgSO_4$, and evaporated in 3-piperidylcarbonyl]-3(S)-ethynyl-ß-alanine ethyl ester bromomethyl-5-methyl-2-oxo-1,3-dioxole (0.19 g) in N,N-After stirring at 0°C for 15 minutes, a solution of 4-[(R)-1-[3-{1-(5-methyl-2-oxo-1,3-dioxol-4-yl-methyl)-4alanine ethyl ester (90 mg) as an oil.

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(8和)数 3.20元3534 (4H, m), 3.51-3.66 (1H, m), 4.06-IR (Film) : 2930, 1810, 1730, 1700, 1655, 1620 cm-1 · 2,23 ((2H公)), 2,21-2,42 (5H, m), 2,65-3,00 (5H, 、J≒7, 0Hz), 1,4551点8Q≤(9H淡面)5,1,90-2,04 (4h, m), 等分类的以供表面), 4.18 (2H, q, J=7.1Hz), 5.05-5.15 JPGR (CDC13, 6): 1.11-1.35 (2H, m), 1.28 (3H, t, (1H, m), 6.65-7.03 (1H, m) Mass (m/r) : 504 (M+1); er

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similar manners to that of Example 37 (1) and Example 21 The following compounds were obtained according to

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piperidylcarbonyl]-3(S)-ethynyl-eta-alanine benzyl(1) N-[(R)-1-{3-(4-piperidyl)propionyl}-3ester trifluoroacetate.

3.62-3.78 (1H, m), 4.10-4.32 (1H, m), 4.87-4.90 IR (KBr) : 3380, 3284, 1780, 1737, 1675, 1623 cm⁻¹ (3H, m), 2.56-3.01 (6H, m), 3.23-3.27 (3H, m), (1H, m), 5.41 (2H, s), 7.37 (5H, m), 8.22 (1H, NMR (DMSO-d6, b): 1.26-1.83 (11H, m), 2.10-2.31 br), 8.49 (1H, br)

Mass (m/z): 454 (M^++1) free of compound

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IR (KBr) : 3409, 3280, 1760, 1673, 1625 cm⁻¹ piperidylcarbonyl]-3(S)-ethynyl-β-alanine]-Mass (m/z): 534 (M^++1) free of compound (cyclohexyloxycarbonyloxy)-1-ethyl ester (2) N-[(R)-1-{3-(4-piperidyl)propionyl}-3trifluoroacetate

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similar manners to that of Example 25 (1) and Example 27. The following compound was obtained according to

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Example 41

 $N^{-1}(R)-1-\{3-(4-piperidy1)propiony1\}-3-$ Piperidylcarbonyl]-3(S)-ethynyl-ß alanine pivaloyloxymethyl ester

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1.95-2.02 (3H, m), 2.54-2.64 (3H, m), 2.78 (1H, m), 3.40-3.47 (2H, m), 3.82-...7 (1H, m), 4.09d, J=2.4Hz), 2.92-3.05 (5H, m), 3.16-3.32 (1H, 4.29 (2H, m), 4.92.5.01 (1H, m), 5.80 (2H, s) NMR (D₂O, 6): 1.20 (9H, s), 1.32-1.82 (7H, m),

Mass (m/z) : 478 (M+1)

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Example 42

 $N=[1-\{3-(4-piperidyl)propionyl\}-3-piperidyl]-3(S)$ benzoylaminosuccinamic acid hydrochloride (245 mg) was

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Example 40

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eluting with (0.1% TPA aqueous solution: CH_3CN = 85:15) to dissolved in water and purified by HPLC on C18 silica gel give N-[1-{3-(4-piperidyl)propionyl}-3-piperidyl]-3(S)benzoylaminosuccinamic acid trifluoroacetate (283 mg).

IR (Film): 2500, 1720, 1610 cm⁻¹

4.29 (total 3H, m), 4.69-4.83 (lH, m), 7.44-7.60 (8H, m), 3.15-3.31 (2H, m), 3.43-3.85 and 4.16-(3H, m), 7.82-7.95 (2H, m), 8.04-8.11 (1H, m), 8.13-8.26 (1H, br), 8.42-8.54 (1H, br), 8.65-NMR (DMSO-d₆, 5): 1.12-1.88 (11H, m), 2.12-3.04 8.74 (1H, m)

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Mass (m/z): 459 (M+1) free of compound

The following compounds were obtained according to a similar manner to that of Example 38 (1)

Example 43

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(2H, m), 1.31-1.37 (6H, m), 1.45 (9H, s), 1.52-4.04-4.15 (3H, m), 4.11 (2H, t, J=6.6Hz), 5.05-1.73 (9H, m), 2.28 (1H, d, J=2, 3Hz), 2, 33-2, 40 (3H, m); 2.60-2.76 (4H, m), 3.19=3.71 (3H, m), WAR (CDCl3, 6): 0.91 (3H, t, J=6.7Hz), 1.01-1.23 piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)-IR (Film) : 2930, 2860, 1720, 1650, 1620 cm-1 (1) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-5-15 (1H, m), 6,67-7.08 (1H, m) ethynyl- β -alanine n-pentyl ester

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(2H, m), 1.27-1.40 (7H, m), 1.45 (9H, s), 1.51-1.79 (10H, m), 2.28 (1H, d, J=2.3Hz), 4.06-4.14 IR (Film) : 2930, 2860, 1720, 1660, 1640, 1620 cm⁻¹ NMR (CDCl₃, 5): 0.89 (3H, t, J=6.6Hz), 1.00-1.22 piperidy1)propiony1!-3-piperidy1carbony1]-3(S)-N-[(R)-1-{3-(1-tert-butoxycarbonyl-4ethynyl- β -alanine n-hexyl ester

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(3H, m), 4.11 (2H, t, J=6.6Hz), 5.05-5.16 (1h, m), 6.72-7.08 (1H, m)

(3) N-[(R)-1-{3-(1-tert-butoxycarbonyl-4-

IR (Film) : 3000, 2980, 2925, 2860, 1730, 1675, piperidyl)propionyl}-3-piperidylcarbonyl]-3(S)ethymyl- β -alamine 4-chlorobenzyl ester 1660, 1620 cm⁻¹

1.39-1.77 (9H, m), 2.27 (1H, d, J=2.3Hz), 2.31-2.39 (3Н, т), 2.60-2.76 (4Н, т), 3.20-3.60 (3Н, m), 3.93-4.14 (3H, m), 5.05-5.19 (1H, m), 5.11 NMR (CDC13, 6): 1.00-1.21 (2H, m), 1.45 (9H, s), (2H, s), 6.86-7.07 (1H, m), 7.33 (4H, s)

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The following compounds were obtained according to similar manner to that of Example 25 (1).

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Example 44

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J=13.3 and 8.1Hz), 8.51-8.69 (1H, br), 8.85-8.96 (3.NMR (DMSO-d6, 6): 0.87 (3H, t, J=5.5Hz), 1.28-1.88 3.32-3.80 (2H, m), 4.03 (2H, t, J=6.5Hz), 4.10-(17H, m), 2.06-2.38 (3H, m), 2.60-3.19 (8H, m), 4.32 (1H, m), 4.79-4.92 (1H, m), 8.53 (1H, dd, piperidylcarbonyl]-3(S)ethynyl- β -alanine n-pentyl IR (KBr, pellet) : 3413, 3041, 2947, 2862, 1734, (1) N-[(R)-1-3-(4-piperidyl)propionyl}-3-1657, 1610 cm-1 ester hydrochloride (1H, br)

IR (KBr) : 3408, 3035, 2958, 2933, 2858, 1736, 1653 Piperidylcarbonyl]-3(S)-ethynyl- β -alanine n-hexyl (. N-[(R)-1-3-(4-piperidy1)propiony1}-3-1616 cm⁻¹ ester hydrochloride

What we claim is:

A compound of the formula:

wherein \mathbb{R}^1 is N-containing cycloalkyl which may have one or more suitable

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 \mathbb{A}^1 is lower alkylene, lower alkanyl-ylidene ${\tt R}^2$ is carboxy or protected carboxy, substituent(s),

or lower alkenylene, each of which may have one or more suitable substituent(s),

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 ${\tt A}^3$ is lower alkylene which may have one or môre suitable substituent(s), A^2 is lower alkylene,

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is a group of the formula:

heterocyclic group which may have one or is N-containing more suitable substituent(s)), wherein

X is O, S or NH,

Y is NH

(wherein \mathbb{R}^3 is hydrogen or lower alkyl),

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J=8.7Hz), 8.47-8.58 (1H, m), 8.47-8.64 (1H, br),

8.80-8.90 (1H, br)

4.09-4.34 (1H, m), 4.82-4.94 (1H, m), 5.11 (2H,

s), 7.40 (2H, d, J=9.0Hz), 7.45 (2H, d,

(3H, m), 2.59-3.10 (7H, m), 3.17-3.31 (3H, m), NMR (DMSO-d6, 6): 1.21-1.84 (11H, m), 2.09-2.36

IR (KBr, pellet) : 3458, 3034, 2949,2862, 1736,

1649, 1618 cm-1

piperidylcarbonyl]-3(S)-ethynyl-ß-alanine 4-

chlorobenzyl ester hydrochloride

(3) N-[(R)-1-{3-(4-piperidyl)propionyl}-3-

!, m and n are each the same or different an integer of 0 or 1,

and a pharmaceutically acceptable salt thereof.

A compound of claim 1,

wherein R¹ is 3 to 8 membered cycloalkyl

which may have one or more suitable containing 1 to 3 nitrogen atom(s) substituent(s),

 ${\tt R}^2$ is carboxy or esterified carboxy,

2

 \mathtt{A}^1 is lower alkylene, lower alkanyl-ylidene or lower alkenylene, each of which

may have one or more suitable

substituent(s),

A² is lower alkylene,

A3 is lower alkylene which may have one or more suitable substituent(s),

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to 4 nitrogen atom(s) which may have one or more suitable substituent(s), heteromonocyclic group containing l unsaturated condensed heterocyclic is saturated 3 to 8 membered

group containing 1 to 4 nitrogen atom(s) which may have or

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more suitable substituent(s) or saturated 3 to 8-membereo heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have one or more suitable

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is 0, S,

substituent(s),

is NH,

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(wherein R^3 is hydrogen or lower alkyl),

l is an integer of 0 or 1,

is an integer of 0 or 1,

is an integer of 0 or 1.

A compound of claim 2,

. ش

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wherein \mathbb{R}^1 is piperidyl which may have 1 or 2 oxo

or [5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl](lower)alkyl,

15

is piperidyl, morpholinyl, tetrahydroquinolyl or

is lower alkylene which may have 1 to 3 suitable substituent(s) selected from edioxy; (C1-C6)alkyl having unsaturated the group consisting of (C1-C6)alkyl; phenyl; phenyl(C1-C6)alkyl; phenyl(C1-C6)alkyl having 1 to 4 (C1-C6)alkoxy, ...halo(C1-C5)alkyl or (C1-C6)alkylene (C2-C6)alkenyl; (C2-C6)alkynyl; pyrrolydinyl, F_A3

20

concaining 1 to 4 nitrogen atom(s); and phenyl(C1-Cf)alkylcarbamoyl; cyano; amino; protected amino; contansed heterocyclic group

25

A², X, Y or Z are each as defined

l is an integer of 0, m is an integer of 0,

A compound of claim 3,

an integer of 0.

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or [5-(lower)alkyl-2-oxo-1,3-dioxolwherein R1 is piperidyl which may have 1 or 2 oxo 4-yl:](lower)alkyl,

is piperidyl, morpholinyl, tetrahydroquinolyl or pyrrolydinyl,

 ${\tt A}^3$ is lower alkylene which may have 1 to 3 phenyl; phenyl(C1-C6)alkyl; phenyl(C1dioxy; (C1-C6)alkyl having unsaturated suitable substituent(s) selected from the group consisting of (C1-C6)alkyl; C6)alkyl having 1 to 4 (C1-C6)alkoxy, halo(C1-C6)alkyl or (C1-C6)alkylene containing 1 to 4 nitrogen atom(s); cyano; amino; (C1-C6)alkanoylamino; hydroxy, (C1-C6)alkoxy, halogen or aroylamino which may have 1 to 3 (C2-C6)alkenyl; (C2-C6)alkynyl; condensed heterocyclic group phenyl; cyclo(C3-

C6)alkoxy(C1-C6)alkylcarbonylamino; phenylsulfonylamino; and phanyl(Cl-C6)alkylcarbonylamino; (C1-(C2-C6)carbonylamino; (C1-C6)alkyľsulfonylamino; C6)alkylcarbamoy1;

25

R2, R3, A1, A2, X, Y or Z are each as defined in claim 3,

l is an integer of 0, n is an integer of 0. m is an integer of 0,

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wherein R^l is piperidyl, A compound of claim 4 ٠. ن

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 ${\tt A}^3$ is lower alkylene which may have lower $^{
m Al}$ is lower alkylene or lower alkanyl-, alkyl, lower alkynyl or lower alkanoylamino, ylidene,

is piperidyl,

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10

 $\rm R^2,\ R^3,\ A^2,\ Y,\ \ell$, m and n are each as defined in claim 4.

 ${\tt A}^3$ is lower alkylene having lower Al is lower alkylene, alkanoylamino, A compound of claim 5, wherein R³ is hydrogen,

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, X, Y and Z are each as defined in claim 5.

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Piperidylcarbonyl]-2(S)-acetylamino-B-alanine N-[(R)-1-{3-(4-piperidyl)propionyl}-3or its hydrochloride

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 ${\tt A}^1$ is lower alkylene, wherein R3 is hydrogen, 8. A compound of claim 5,

30

, X, Y, Z, t, m and n are each A³ is lower alkylene having lower alkynyl,

as defined in claim 5.

Piperidylcarbonyl]-3(S)-ethynyl-B-alanine N-[(R)-1-{3-(4-piperidyl)propionyl}-3-

A compound of claim 4, wherein R^1 is piperidyl, . 10

A³ is lower alkylene which may have lower A¹ is lower alkylene or lower alkanylalkyl, lower alkynyl or lower alkanoylamino, ylidene,

2

s morpholinyl,

 $R^2,\ R^3,\ A^2,\ Y,\ \ell$, m and n are each as defined in claim 4.

Al is lower alkylene, A compound of claim 5, wherein R³ is hydrogen, Ξ:

20

A³ is lower alkylene,

, X, Y and 2 are each as defined in claim .10.

N-[4-{3-(4-piperidyl)propionyl}-2morpholinylcarbonyl]-8-alanine or its.hydrochloride

A process for preparing a compound of the formula 13.

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wherein \mathbb{R}^1 is N-containing cycloalkyl which may have one or more suitable substituent(s),

or lower alkenylene, each of which may ${\bf A}^1$ is lower alkylene, lower alkanyl-ylidene \mathbb{R}^2 is carboxy or protected carboxy, have one or more suitable substituent(s),

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 ${\tt A}^3$ is lower alkylene which may have one or more suitable substituent(s), ${\tt A}^2$ is lower alkylene,

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is a group of the formula:

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heteroyclic group, which may have one or is N-containing more suitable substituent(s)), wherein

is O, S or MH,

in and n are each the same or different an (wherein R^3 is hydrogen or lower alkyl), integer of 0 or 1,

and a salt thereof, which comprises

35

(i) reacting a compound of the formula :

$R^{1}-(x)_{\rho}-A^{1}-COOH$

wherein \mathtt{R}^1 , \mathtt{A}^1 , X and ℓ are each as defined above, or a salt thereof, with a compound of the formula or its reactive derivative at the carboxy group

$$HN \longrightarrow (A^2)_{n} z - A^3 - R^2$$

10

wherein R^2 , A^2 , A^3 , HN, Z and R are each as defined above,

or its reactive derivative at the amino group or a salt thereof, to give a compound of the formula :

$$R^{1-(x)} + A^{1-c-N} - (A^{2}) + 2A^{3-R^{2}}$$

20

wherein R^1 , R^2 , A^1 , A^2 , A^3 ,-N \rightarrow , X, Z, ℓ and n are each as defined above, or a salt thereof, or:

(11) reacting a compound of the formula :

wherein R^1 , A^1 , A^2 , -N, N, N, and n are each as defined above,

or a salt thereof, with a compound of the formula : Or its reactive derivative at the carboxy group

| : HN-A³-R²

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wherein R^2 , R^3 and A^3 are each as defined above, or its reactive derivative at the amino group or a salt thereof, to give a compound of the formula :

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wherein R^1 , R^2 , R^3 , A^1 , A^2 , A^3 , -N \longrightarrow , X, ℓ and nor a salt thereof, or

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(iii) reacting a compound of the formula :

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$$R^{1-\{X\}} \frac{A^{1-C-\{Y\}}}{1}$$
 NH

Wherein R^1 , A^1 , $HN \longrightarrow X$, X, Y, ℓ and m are each as defined above,

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or ϵ salt thereof, with a compound of the formula : or its reactive derivative at the amino group

R2-A3-CCUH

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or its reactive derivative at the carboxy group or salt thereof, to give a compound of the formula : wherein \mathbb{R}^2 and \mathbb{A}^3 are each as defined above,

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, X, Y, & and m are wherein R^1 , R^2 , A^1 , A^3 , -N or a salt thereof, or

(iv) subjecting a compound of the formula :

10

$$x_3^1 + x + \frac{1}{t} - x^1 - c + x + \frac{N}{m}$$

15

amino protective group, which may have 7 X, Y, Z, l, m and n are one or more suitable substituent(s), or a salt thereof, to elimination reaction of the amino protective group, to give a compound of the Ra is N-containing cycloalkyl having each as defined above, and wherein R², A¹, A³,

20

$$R_{b}^{1}(x) = A^{1} - C + (Y^{2}) + (A^{2}) + (A^{2})$$

X, Y, Z, l, m and n are each as defined above, and wherein R^2 , A^1 , A^2 , A^3 ,

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 $_{\mathrm{D}}^{\mathrm{Rl}}$ is N-containing cycloalkyl which may have one or more suitable substituent(s),

or a salt thereof, or

(v) subjecting a compound of the formula ;

$$R^{1-(x)} + A^{1-c-(x)} + A^{2} + A^{2-2-A^3-R_a^2}$$

10

, X, Y, Z, &, m and n are each as defined above, and wherein R^1 , A^1 , A^2 , A^3 ,

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or a salt thereof, to elimination reaction of carboxy protective group, to give a compound of the formula : R_a^2 is protected carboxy,

$$x^{1} - (x) + x^{1} - (x) + x^{2} + x^{2} + x^{2} - (x) + x^{2} + x^$$

20

'X, Y, Z, l, meand n re each as defined above, or a saltthereof, or wherein R¹, A¹, A², A³,

(vi) subjecting a compound of the formula

30

$$R_{b}^{1} + K + \frac{1}{\ell} - C + K + \frac{N}{m} + \frac{N}{n} + A^{2} + C - A^{3} - R^{2}$$

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, X, Y, Z, l, m and n , may have one or more suitable is N-containing cycloalkyl which are each as defined above, and substituent(s), wherein R2, A¹, A², A³, RD 13

or a salt thereof, to protecting reaction of amino, to give a compound of the formula:

$$R_{a}^{1} + (x_{1}^{1} - x_{1}^{-1} - (x_{1}^{-1}) + (x_{2}^{1} - x_{1}^{-1} - x_{2}^{-1} - x_{2}^{-1} - x_{2}^{-1} + x_$$

10

amino protecting group, which may have , X, Y, Z, 8, m and one or more suitable substituent(s), are each as defined above, and Ra is N-containing cycloalkyl having wherein R^2 , A^1 , A^2 , A^3 , or a salt thereof, or

15

(Vii) subjecting a compound of the formula :

20

$$R^{3}-(x) \frac{1}{\ell} - x^{1} - x^{2} - (x) \frac{1}{\ell} \frac{1}$$

25

or its reactive derivative at the carboxy group or a salt thereof, to protecting reaction of the carboxy, 7, X, Y, Z, 8, m and n are each as defined above, to give a compound of the formula : wherein R^1 , A^1 , A^2 , A^3 , -

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$$(1-(x) \frac{1}{\ell} - x^{1} - c - (x) \frac{1}{\ell} + x^{2} - x^{2} - x^{3} - x^{2}$$

- - X, X, Z, 8, m and n are each as defined above, and R_a^2 is protected carboxy, wherein R^1 , A^1 , A^2 , A^3 ,

or a salt thereof, or

10

(Viii) subjecting a compound of the formula :

$$R^{1-\{X\}} \xrightarrow{\ell} A^{1-C-\{Y\}} \xrightarrow{\ell} A^{2} \xrightarrow{r} Z^{-A} \xrightarrow{3-R^{2}} R^{2}$$

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protective group, to give a compound of the formula : $\mathbf{A}^3_{\mathbf{a}}$ is lower alkylene having protected amino or a salt thereof, to elimination reaction of amino ←, x, Y, Z, ℓ,m and n are each as defined above, and wherein R^1 , R^2 , A^1 , A^2 ,

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$$R^{1}-(x)_{p}-A^{1}-C-(x)_{m}$$
 $(A^{2})_{n}-(x)_{n}-(x)_{p}-(x)_{p}-(x)_{p}$ $(A^{2})_{n}-(x)_{p}-(x)_{p}$

are each as defined above, and λ_b^3 is lower alkylene having amino or a salt thereof, or wherein R^1 , R^2 , \tilde{A}^1 , A^2 , \leftarrow

30

(ix) subjecting a compound of the formula:

35

X, Y, Z, &, m and n or a salt thereof, to acylation reaction of amino, to $A_{\rm b}^{\rm 3}$ is lower alkylene having amino, are each as defined above, and give a compound of formula : wherein R1, R2, A1, A2,

10

$$(1-(x)_{\ell}^{-}A^{1}-C-(x)_{m}^{-}C)$$

, X, Y, Z, l, m and n A³ is lower alkylene having acylamino, are each as defined above, and wherein R^1 , R^2 , A^1 , A^2 , or a salt thereof.

20

- pharmaceutically acceptable salt; thereof in admixture A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a with pharmaceutically acceptable carriers or excipients.
- Use cf a compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament 15.
- acceptable salt thereof for use as a medicament. A compound of claim 1 or a pharmaceutically
- A method for the prevention and/or the treatment of 17.

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diseases caused by thrombus formation; restenosis or inflammation; immune diseases; or metastasis; or for compound of claim 1 or a pharmaceutically acceptable vascular surgery, valve replacement, extracorporeal reocclusion; the thrombus formation in case of the adjuvant therapy with thrombolytic drug or anticoagulant; which comprises administering a circulation or transplantation; disseminated thrombocytopenic; essential thrombocytosis; salt thereof to a human being or an animal. intravascular coagulation; thrombotic

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REPORT
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PCT/JP 94/01550 Inte. onal Application No

Relevant to claim No. 1-17 1-17 A61K31/445 Y Petent family members are listed in annex. Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C07D405/12 cited in the application
see RN 138108-54-0, .beta.-Alanine, N-[[1[3-[1-[[(1,1-dimethylethoxy)carbonyl]amin
o][[(1,1-dimethylethoxy)carbonyl]imino]me
thyl]-4-piperidinyl]-1-oxopropy]3-piperidinyl]carbonyl]-, phenyl According to International Patent Gassification (IPC) or to both national classification and IPC Category * | Citation of document, with indication, where appropriate, of the relevant passages B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 CO7D CO7K EP.A.0 512 831 (MERCK) 11 November 1992 cited in the application see the whole document EP,A,O 445 796 (HOFFMANN-LA ROCHE) 11 September 1991 C07D401/12 Further documents are listed in the continuation of box C. CO7K5/06 CO7D211/56 C. DOCUMENTS CONSIDERED TO BE RELEVANT A. стазянсатом ор subject 1рс 6 с070211/60 с070401/06

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Kissler, B Authorized officer Name and mailing address of the ISA
European Patento Office, P. B. 1811 Patentiann 2
NL. - 1220 HV Billynin,
Tel. (+ 31-70) 340-2546, Tr. 31 631 epo m,
Fac (- 31-70) 340-2546 3 January 1995

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INTERNATIONAL SEARCH REPORT

information on patent family members

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